ARTERIAL AUSCULTATION

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THE art of auscultation appears to have reached its peak about one generation ago; in the period after the first world war radiology was rapidly advancing but physicians were still prepared to base a firm diagnosis of a pulmonary or cardiac lesion upon their clinical findings including auscultation. Today, an X-ray is an essential part of such a diagnosis. This advance of diagnostic radiology has led to a decline in the importance of auscultation. In the radiological department of one of the best hospitals in the world a stethoscope hangs on the wall and below it is written:

"Rare and unusually well-preserved fragments known as the 'stethoscope' (binaural type), circa 1918 formerly in common use in the diagnosis of pulmonary and cardiac disease.

"This contraption was developed by Lænnec early in the 19th century and was actually in general use until the rœntgen era."

The auscultation of arteries, apart from those close to the heart and those involved by arteriovenous fistulæ or aneurysms, has never been widely practised, but valuable information may be obtained by this simple means. In our view the findings on auscultation of the peripheral arterial system, when taken in conjunction with other information obtained by a full clinical examination, can often enable the clinician to make an accurate diagnosis, and in many patients this simple test may permit the omission of arteriography, an expensive and time-consuming investigation, which is not always without risk.

The findings on auscultation in patients with arterial aneurysms, arteriovenous fistulæ, and coarctation of the aorta are well known and will not be discussed again, but the findings in patients with *atherosclerosis* have received much less attention. Arterial stenosis when caused by a plaque of atheroma at the origin of the internal carotid will, if the stenosis is of sufficient severity to cause symptoms, produce a systolic murmur in at least a quarter of these patients (Rob 1959).

Occasionally a systolic murmur extending into the first part of the diastole may be due to the development of an unusually efficient collateral circulation around a complete arterial occlusion and may be heard over the collateral arteries. The diagnosis of atherosclerotic arterial disease at the stage of arterial stenosis as opposed to complete arterial thrombosis is becoming increasingly important. This is particularly so in the case of the carotid, vertibral, mesenteric, and renal arteries and the vessels of the limbs. *Carotid arterial stenosis* usually occurs because a plaque of atheroma forms at the origin of the internal carotid artery; such a stenosis may produce clinical effects which are indistinguishable from those caused by a complete thrombosis of this artery. The importance of arterial auscultation in this instance is that it may make possible the clinical differentiation of a complete from a partial occlusion of the cervical portion of the internal carotid artery. This systolic murmur is heard over the bifurcation of the carotid artery in the neck; a murmur of this type was present in 59 of 103 patients with a proved stenosis of this artery; it is easily distinguished from the full-cycle systolic and diastolic murmurs heard at this site in many patients with a carotid-body tumour. In no case of complete internal carotid occlusion was this murmur heard, but in one patient a similar murmur was heard from a stenosis involving only the origin of the external carotid artery. A venous hum in the lower part of the neck is sometimes confusing, especially as the systolic accentuation is often marked. Normally the hum is a systolodiastolic murmur. Light pressure on the deep veins above the point of application of the stethoscope abolishes this sort of murmur. In 3 patients a similar murmur heard at the base of the neck has been shown to be due to a stenosis at the origin of the *vertebral artery*. In addition these murmurs may be heard in patients without any clinical abnormalities; the reason here is probably an arterial stenosis which has not as yet caused symptoms, though it is possible that murmurs in the neck may be produced in arteries which are tortuous and not stenosed.

Another site where arterial auscultation is of special value is the *renal artery*. Stenosis of a renal artery is a cause of arterial hypertension and often produces a systolic murmur which can best be heard by pressing the stethoscope firmly against the abdominal wall about 1 to 2 inches above and 1 inch to the right or left of the umbilicus. This murmur when present often enables the clinician to decide not only that the patient has an arterial stenosis at this site but occasionally in which renal artery the stenosis lies. While murmurs may arise in other arteries deep to the epigastrium, the murmur has been observed to disappear after thrombosis in or reconstruction of the renal artery, thus proving its origin (Peart 1959). The great value of this murmur is in screening patients with unexplained hypertension. In these patients the possibility that stenosis of a renal artery is the cause must always be considered, but a firm preoperative diagnosis can only be made by divided renal-function studies, and aortography or renal arteriography, major investigations which cannot be performed on every patient. When this murmur is present a clinician can request a renal arteriogram in the knowledge that this investigation will be positive in many cases. 7 consecutive cases of renal artery stenosis studied at this hospital had such a murmur.

Auscultation along the course of the *abdominal aorta* and *iliac*, and *proximal femoral arteries* is also a useful investigation. A systolic murmur indicates the exact site of an area of arterial stenosis. In many patients with arterial disease in the limbs no murmurs will be heard because a complete arterial occlusion is present, but in some patients with unilateral symptoms auscultation of the arteries in the sound limb will reveal a systolic murmur which may indicate an arterial stenosis, a possible site for a thrombosis at some future date. In the upper limb the greatest use for arterial auscultation is in patients with the *aortic-arch syndrome* and *cervical ribs* or the *thoracic-outlet syndrome*, here a systolic murmur over the subclavian artery is a common finding not only when

a fusiform aneurysm has formed but before this when the artery is still normal on palpation. At this stage the systolic murmur indicates roughness and irregularities on the wall of the artery usually associated with some mural thrombosis. A systolic murmur over the subclavian artery in the root of the neck is a common finding with no evidence of disease, especially if the stethoscope is applied heavily. Irregularities in the arterial wall or dilatation lead to loud long murmurs.

Auscultation of arteries is also of value both during and after surgical operations. During an operation a sterile stethoscope may be a useful aid in the sometimes difficult task of accurately locating an arteriovenous fistula or, in the case of visceral arteries, the exact point of an arterial stenosis. The exact location of stenosis of the renal or mesenteric arteries by this means is of special value. Another use of arterial auscultation is in the postoperative period. After an arterial reconstruction operation (thromboendarterectomy, direct suture or insertion of an arterial substitute) the artery should be silent, but if there is a stenosis at the site of an anastomosis or a kink in an arterial graft a murmur will be produced. Such a murmur indicates strongly that this artery is likely to thrombose eventually.

Conclusion

The auscultation of arteries is a worth-while investigation, particularly in patients who may have an arterial stenosis caused by atherosclerosis.

REFERENCES

Peart, W. S. (1959) *Brit. med. J.* ii, 1353.
Rob, C. G. (1959) *Proc. R. Soc. Med.* **52**, 549.

POSTOPERATIVE PROPHYLACTIC ANTICOAGULANTS

FIVE-YEAR STUDY IN AN OBSTETRIC AND GYNÆCOLOGICAL UNIT

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MASSIVE pulmonary embolism is now one of the commonest causes of death in the postoperative period (*Lancet*, 1957).

For example, in a general hospital with about 200 surgical beds, about 7 fatal cases of pulmonary embolism may be expected each year despite early ambulation and rigorous anticoagulant therapy (Marks et al. 1954). This is probably due to the high incidence of fatal cases of pulmonary embolism in which there are no premonitory symptoms or signs.

We describe here the results of five years' experience of prophylaxis with anticoagulants.

Material and Methods

With present facilities and laboratory staff it is impossible to administer prophylactic anticoagulants to every surgical patient even if this were desirable. Several workers have attempted to estimate a prethrombotic tendency of the blood, but critical analysis suggests that the methods so far described offer no help in choosing patients for routine anticoagulant therapy.

Published reports and our experience in Cambridge suggested that the incidence of thromboembolic disease was highest after gynæcological and obstetric operations, and such cases have therefore been selected for this study.

Prophylactic anticoagulants have been administered to selected groups of cases in the United Cambridge Hospitals: (1) major gynæcological operations in patients over the age of 40; (2) all cæsarean sections; (3) operative procedures for malignant disease of the genital tract at any age; (4) any major gynæcological or obstetric operation irrespective of age when there was a previous history of thrombophlebitis.

Phenindione (' Dindevan ', Evans) was used throughout the trial. The initial dose was administered on the third day after operation and varied with the age of the patient: under 45 years, 200 mg.; 46–55, 150 mg.; 56–65, 100 mg.; over 65, 50 mg. Subsequent doses were administered daily to maintain the prothrombin concentration (Quick's one-stage method) at 15–30%. Treatment was continued until the tenth postoperative day in all cases. It was prolonged beyond this if the patient was still confined to bed.

TABLE I—TYPE OF OPERATION AND AGE OF PATIENTS STUDIED

Operation	No.	Age-groups
Abdominal hysterectomy	836	556 under 45 yr.; 1004 45 yr. or over
Vaginal hysterectomy	45	
Pelvic floor repair	501	
Simple and radical vulvectomy	29	
Abdominal sterilisation	41	
Miscellaneous	108	
Cæsarean section	317	All under 45 yr.
Total	1877	—

Results

In the five years June, 1953, to June, 1958, 1877 patients were treated with prophylactic anticoagulants. 1560 were gynæcological patients and 317 had undergone cæsarean section (table I).

In order to evaluate prophylactic anticoagulant therapy a comparison was made with the figures for the period 1947–53. During the entire period 1947–58 the number of admissions, the types of cases relative to disease, age and operation, and the postoperative care did not appreciably alter.

In the years 1947–48 early ambulation was the rule, but no anticoagulants were used. Between 1949 and 1953 anticoagulants were given therapeutically to all patients with thromboembolic disease, but prophylactic anticoagulants were not administered.

TABLE II—EFFECT OF THERAPEUTIC MEASURES ON INCIDENCE OF THROMBOEMBOLIC DISEASE: GYNÆCOLOGICAL AND OBSTETRIC PATIENTS

Year ended June 1	Measures	Venous thrombosis	Pulmonary embolism		Total
			Non-fatal	Fatal	
1947	No anticoagulants	•	•	1	•
1948		•	•	2	•
1949	Therapeutic anticoagulants	26	4	3	33
1950		42	5	1	48
1951		32	3	2	37
1952		23	6	1	30
1953		36	3	2	41
1954	Prophylactic anticoagulants	6	1	0	7
1955		5	1	1	7
1956		8	1	0	9
1957		4	2	1	7
1958		1	1	0	2
Averages: 1949–53		31·8	4·2	1·8	37·8
1954–58		4·8	1·2	0·4	6·4

• Data insufficiently accurate.

TABLE III—MORTALITY DUE TO THROMBOEMBOLIC DISEASE

Types of cases	1949–53				1954–58			
	Total admissions	Fatal thromboemboli			Total admissions	Fatal thromboemboli		
		Total	No. per yr.	No. per 100 admissions		Total	No. per yr.	No. per 100 admissions
General surgical	13,008	30·0	6·0	0·23	15,424	44·0	8·8	0·29
General medical	7962	15·0	3·0	0·19	9593	28·0	5·6	0·29
Gynæcological (including cæsarean sections)	4574	9·0	1·8	0·20	5264	2·0	0·4	0·04

Only cases of embolism in which the pathologist considered at necropsy that this was the main cause of death are included.

Coincident with the use of prophylactic anticoagulants, the total incidence of thromboembolic disease fell from an average of 38 cases per annum for the period 1949–53 to 6 per annum for 1953–58. The fatal-pulmonary-embolism-rate per annum fell from 1·8 to 0·4 in the corresponding period. The greatest change has occurred in the incidence of deep vein thrombosis—a fall from 159 cases to 24 (table II).

The incidence of fatal pulmonary embolism in general surgical and general medical patients in the same hospital shows no similar change (table III).

Of the 32 patients who developed thromboembolic disorders, 11 were not being treated with anticoagulants at the time of the episode. In 32 the incident occurred before the third day and in 6 after the twelfth day; 2 were omitted from treatment in error. Of the 21 patients who were receiving anticoagulants 16 had a prothrombin content of over 30% at the time of the episode.

Hæmorrhage

There were 57 episodes of bleeding. 21 required no active treatment and anticoagulants were not discontinued. In 26 local measures (e.g., hot vaginal douches and gauze packs) were employed and anticoagulants were discontinued. No steps, however, were taken to reverse the lowered prothrombin level. In 10, severe hæmorrhage necessitated transfusion in addition to the local measures. It was also considered expedient to raise the prothrombin level by the immediate administration of vitamin K ('Konakion').

Discussion

Incidence of Postoperative Thromboembolism

It is difficult to establish accurately the incidence of postoperative thromboembolism because of the considerable variation in figures from different centres. deBakey (1954), reviewing over 3 million operations, concluded that the average incidence of fatal postoperative embolism was 0·14% with a range 0·01 to 0·87%, and of total thromboembolic disease about 1·2%.

Gynæcological operations have a higher incidence of thromboembolism than any other individual group: an incidence of 3·5% overall and of fatal pulmonary emboli about 0·4% (Barker 1944, Zilliacus 1946, Allen et al. 1947, Ochsner et al. 1951, Schubert and Uhlmann 1954). For abdominal hysterectomy in patients over the age of 50 years an incidence of 1·26% fatal pulmonary emboli has been reported (Barker et al. 1940).

These figures agree very closely with those found in Cambridge during the period 1947–53.

Pulmonary Embolism

Unfortunately the majority of fatal pulmonary emboli are preceded by no premonitory symptoms or signs.

Belt (1934) could find no clinical evidence of thromboembolic disease in about 90% of the 56 patients with fatal pulmonary emboli; Barker et al. (1941) in 85% of 343 cases; and Crane (1957) in 66% of his cases. Gibbs (1957) has, however, shown that despite the lack of clinical evidence careful necropsy examination reveals a leg-vein thrombosis in a high proportion.

In a previous Cambridge study (Marks et al. 1954) over 80% of the patients in whom a fatal pulmonary embolism occurred showed no symptons or signs during life.

These findings suggest that fatal pulmonary embolism cannot be prevented solely by the treatment of pre-existing peripheral thrombosis and that some other method must be found.

Three main methods have been advocated: (1) early full ambulation, (2) elastic bandages or stockings, (3) anticoagulants.

Early ambulation reduces the incidence of pulmonary embolism but does not wholly prevent it. The use of elastic stockings and bandages for prophylaxis was not considered practicable. Prophylactic anticoagulant therapy has been widely used on the Continent, with varying results—a variation that may be due to differences in method (deBakey 1954).

A review of fatal pulmonary embolism in surgical cases between 1947 and 1953 showed that over 50% took place between the fifth and the twelth postoperative day. The remainder occurred after the twelfth day in patients immobilised in bed for a long time. This accords with the results of Barker et al. (1941), who from thirteen years' records at the Mayo Clinic found that 52·5% of the surgical thromboembolic complications and 52·6% of fatal postoperative pulmonary emboli occurred between the fifth and the twelfth day.

The incidence of fatal pulmonary embolism is higher in older people, and it was found from the Cambridge records that over 90% were over 40 years of age. Other factors which predispose to fatal pulmonary embolism are infection, carcinoma, severe varicose veins, and heart-failure (Barker et al. 1941).

We therefore decided to administer prophylactic anticoagulants to patients over the age of 40, and to carcinoma patients at any age, from the third to the tenth post-operative day inclusive. This ensured that during the critical fifth to twelfth day the patient would have reduced blood coagulability.

Prophylactic Anticoagulants

Table II shows that the total incidence of thromboembolism and the incidence of fatal pulmonary embolism have been considerably reduced during the five years that prophylactic anticoagulants have been administered. This is not a fully controlled study because we did not feel justified in withholding prophylaxis from about 1000 patients. Nevertheless, the incidence of fatal pulmonary embolism in general surgical and medical cases during this period increased slightly (table III), while the incidence in the patients receiving anticoagulants was reduced to a fifth of the previous average.

From the findings in the 32 cases showing thromboembolic complications it appears that for adequate

prophylaxis a prothrombin content below 30% is desirable, but occasional patients (4 in our series) will not be protected even at this level.

The thromboembolic cases occurred predominantly during two periods. Period 1 was during the first six months when our dosage was experimental; period 2 coincided with a reduction in the number of laboratory estimations in the interests of economy. As a result of this we are convinced that good results can be achieved only with careful attention to dosage and adequate laboratory control. We regard a prothrombin level of 20–30% as optimal, and to ensure the maintenance of this level three to five prothrombin estimations are essential during the eight-day period.

Hæmorrhage

From the early days of the trial it was obvious that any bleeding, however trivial, would be attributed to anticoagulant therapy. In the 10 cases of severe hæmorrhage we consider that sepsis (evidenced by a febrile postoperative course or local tissue necrosis) was a major contributory factor, but we are convinced that bleeding is enhanced by the lowered blood-prothrombin level.

Conclusions

On the basis of experience in over 1800 patients over the past five years the following conclusions may be drawn:

(1) For adequate prophylaxis the blood-prothrombin content must be kept below 30%, while to avoid hæmorrhage it should not fall below 15%.

(2) Control of the blood-prothrombin level necessitates frequent estimations.

(3) The time and cost involved, coupled with the risk of hæmorrhage, makes it unjustifiable to use this method routinely in general surgery.

(4) The results suggest that prophylactic anticoagulants have a limited place in certain patients who have undergone operation: particularly those who have had abdominal operations and who have cardiac insufficiency, a previous history of thrombophlebitis, or bad varicose veins.

(5) In gynæcology the results justify adoption of the method as a routine postoperative procedure in view of the known high incidence of thromboembolism.

Summary

Five years' experience of the use of prophylactic anticoagulants in 1877 gynæcological and obstetric postoperative patients is reported.

The patients received phenindione from the third to the tenth postoperative day in doses to maintain the prothrombin levels at between 15 and 30%.

The incidence of thrombotic disease was reduced by a factor of five. It is concluded that anticoagulants should be administered routinely after gynæcological operations and in selected general-surgical cases.

REFERENCES

Allen, E. V., Hines, E. A., Kvale, W. F., Barker, N. W. (1947) *Ann. intern. Med.* **27**, 371.
Barker, N. W. (1944) *Minn. Med.* **27**, 102.
— Nygaard, K. K., Walyers, W., Priestley, J. T. (1940) *Proc. Mayo Clin.* **15**, 769.
— — — — (1941) *ibid.* **16**, 1, 17.
Belt, T. H. (1934) *Amer. J. Path.* **10**, 129.
Crane, C. (1957) *New Engl. J. Med.* **257**, 147.
deBakey, M. E. (1954) *Surg. Gynec. Obstet.* **98**, 1.
Gibbs, N. M. (1957) *Brit. J. Surg.* **45**, 209.
Lancet (1957) ii, 1101.
Marks, J., Truscott, B. M., Withycombe, J. F. R. (1954) *Lancet*, ii, 787.
Ochsner, A., deBakey, M. E., deCamp, P. T., da Rocha, E. (1951) *Ann. Surg.* **134**, 405.
Schubert, G., Uhlmann, G. (1954) *in* Thrombose und Embolie: Hamburger Symposion (edited by F. Beckermann, R. Jürgens, and G. Schubert); p. 65. Stuttgart.
Zilliacus, H. (1946) *Acta. med. scand.* suppl. 171.

THE USE OF VASOPRESSIN ('PITRESSIN') IN THE CONTROL OF BLEEDING FROM ŒSOPHAGEAL VARICES

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THE emergency treatment of bleeding from œsophageal varices in patients with hepatic cirrhosis is unsatisfactory. Œsophageal tamponade by the Sengstaken compression tube (Sengstaken and Blakemore 1950), although initially successful in controlling hæmorrhage, has many complications including a high incidence of œsophageal ulceration (Read et al. 1960). Furthermore, it is extremely unpleasant for the patient, who often refuses to have the tube reinserted if bleeding recurs, and is so demanding on medical and nursing attention that in many hospitals its use is not feasible. Many of these patients are in an advanced state of liver failure, and hæmorrhage is as much a manifestation of this as of portal hypertension; they are therefore usually unsatisfactory risks for emergency surgical treatment.

In 1956, Kehne et al. reported that vasopressin ('Pitressin') would control hæmorrhage from œsophageal varices by lowering the portal pressure, and in 1959 this effect was confirmed by Schwartz and others. The purpose of this paper is to report the use of pitressin in 8 patients with bleeding œsophageal varices.

Methods and Results

Patients

8 patients with bleeding from œsophageal varices associated with cirrhosis and portal hypertension were studied (table 1). All the patients had failed to stop bleeding after blood-transfusion. Varying degrees of liver failure were shown by precoma, jaundice, and ascites with a raised serum-bilirubin and a lowered serum-albumin level. None was considered fit for emergency surgical procedures.

Treatment

Vasopressin is said to constrict coronary arteries (Ruskin 1947) and a preliminary electrocardiogram was taken in every instance. The tracings failed to demonstrate myocardial changes.

Vasopressin 20 units in 1 ml. was diluted in 100 ml. of 5% dextrose and was given intravenously over a ten-minute period. The stomach was aspirated every 30 minutes through a Ryle's tube. Control of hæmorrhage was estimated by disappearance of blood from the gastric juice and by serial pulse and blood-pressure recordings. Portal pressure was measured indirectly in 5 patients by percutaneous splenic puncture with recording of the intrasplenic pressure (Atkinson and Sherlock 1954) and in 2 patients by measurement of the wedged hepatic-vein pressure following hepatic-vein catheterisation (Myers and Taylor 1951, Paton et al. 1953, Taylor and Myers 1956, Reynolds et al. 1957). The catheter was then withdrawn into the innominate vein and used for intravenous therapy. All pressures were recorded with an Elema-Schonander pressure transducer and electromanometer with zero reference set at 5 cm. below the sternal angle

TABLE I—PATIENTS STUDIED AND DURATION OF BLEEDING BEFORE ADMINISTRATION OF VASOPRESSIN AND ITS EFFECT

Case	Age and sex	Ætiological factors	Serum-bilirubin (mg. per 100 ml.)	Serum-albumin (g. per 100 ml.)	Ascites	No. of vasopressin infusions	Before vasopressin		After vasopressin	Comment
							Duration of bleeding (hr.)	Blood transfused (ml.)	Re-bleeding	
1	F 50	Alcohol	2·7	2·3	+	1	48	4000	0	Portacaval anastomosis performed. Alive 1 year later.
2	M 34	Post-hepatitis	3·7	2·5	+++	1	12	2000	0	Portacaval anastomosis performed. Died 1 month later in coma.
3	M 63	Alcohol	2·7	2·7	0	1	72	5000	0	Died 2 weeks later with bronchopneumonia. No further bleeding.
4	M 65	Alcohol	13·4	2·5	++	2	24	3000	+	Re-bled once at 36 hr. Died 8 days later in coma. No further bleeding.
5	F 62	Unknown	10·6	2·3	++	4	12	2000	+	Numerous bleeds initially controlled by vasopressin. All eventually died 5-8 days afterwards with large terminal hæmorrhage.
6	F 73	Alcohol	30·0	2·8	++	6	6	2000	+	
7	F 60	Alcohol	10·1	2·4	0	8	24	3000	+	
8	M 52	Alcohol	5·5	2·3	0	2	12	2000	+	

with the patient supine. Pressures were recorded before and immediately following the vasopressin infusion.

The routine treatment for impending hepatic coma was always followed. This included intravenous hypertonic glucose infusions into a main vein, attention to electrolyte balance, neomycin 4 g. daily by mouth, and enemata (Sherlock et al. 1956).

Control of Hæmorrhage

Before the administration of vasopressin there had been clinical evidence of bleeding for an average time of sixteen hours (range six to seventy-two hours) and a mean of 2500 ml. blood (range 1000 to 5000 ml.) had been transfused (table I). Following the vasopressin, gastric aspirations became clear of blood within one hour and pulse and blood-pressure were maintained without further transfusion in all cases. In 3 patients (cases 1, 2, and 3) hæmorrhage did not recur and 2 of them became suitable for portacaval anastomosis. In 1 of these patients (case 1) a Sengstaken tube had failed to control bleeding before the administration of vasopressin and at operation large gastric varices were seen. In 2 patients (cases 6 and 7) bleeding recurred within four hours and in 3 patients within one to eight days (cases 4, 5, and 8). In 1 of these patients (case 4) vasopressin again controlled the bleeding but the patient died eight days later in coma. At necropsy blood could not be seen in the gastrointestinal tract. Vasopressin was again initially successful in the other 4 patients who re-bled, but bleeding recurred at more frequent intervals, and although vasopressin was given repeatedly at four-hourly intervals they all died with a terminal massive hæmorrhage.

Illustrative Cases

Case 1.—A fifty-year-old housewife was admitted to hospital with jaundice and ascites. Hepatic biopsy confirmed the diagnosis of portal cirrhosis and this was related to a heavy alcohol intake for many years. Barium swallow revealed large œsophageal varices. While under treatment with a low-sodium diet and diuretics, she had a sudden large hæmatemesis and became shocked. A Sengstaken tube was inserted and blood-transfusion commenced. Over the next forty-eight hours her gastric aspirations remained bloodstained and she received 4000 ml. of blood. At this stage the Sengstaken tube was clearly not controlling the bleeding so it was deflated. The intrasplenic pressure was recorded as 25 mm. Hg, and her systemic blood-pressure was at its basal level of 120/90. 20 units of vasopressin in 100 ml. of 5% dextrose were administered intravenously over ten minutes, during which time her systemic blood-pressure rose to 170/100 and fell again to 115/85. She experienced some abdominal discomfort and evacuated a large melæna stool, but 15 minutes after starting pitressin the side-effects had passed off; the intrasplenic pressure had fallen to 15 mm. Hg. A slow 5% dextrose infusion was continued and one hour later her gastric aspiration was clear of macroscopic blood for the first time in forty-eight hours and her pulse and blood-pressure were satisfactory. She showed no further evidence of bleeding.

The electroencephalogram one week later showed a stable rhythm and percutaneous splenic venography revealed a patent portal vein. An end to side portacaval anastomosis was performed and large gastric varices were noted. Her postoperative recovery was uneventful apart from transient ankle œdema. Her ascites has not returned and nine months later she is alive and doing housework.

Comment.—In this patient bleeding was not controlled by the Sengstaken tube presumably because it was coming from large gastric varices. Vasopressin lowered portal pressure and controlled the hæmorrhage satisfactorily so that she improved sufficiently to permit a successful portacaval anastomosis to be performed.

Case 7.—A sixty-year-old woman journalist with a considerable alcoholic history was admitted to hospital for investigation of persistent ankle œdema, jaundice, and bizarre behaviour. Two years previously she had had a subtotal gastrectomy for a low-grade carcinoma of the stomach and the liver was noted to be cirrhotic, this impression being confirmed by biopsy.

A diagnosis of chronic portal systemic encephalopathy (Summerskill et al. 1956) was made, and her mental state improved considerably when dietary protein was restricted and neomycin given. A barium swallow demonstrated prominent œsophageal varices, but the stomach remnant showed no evidence of recurrence of the cancer.

After two weeks in hospital she had a hæmatemesis and over the next twenty-four hours 3000 ml. blood was transfused. In

TABLE II—EFFECT OF VASOPRESSIN (20 UNITS INTRAVENOUSLY IN 10 MINUTES) ON PORTAL PRESSURE MEASURED BY INTRASPLENIC PRESSURE OR BY WEDGED HEPATIC-VEIN PRESSURE

Case	Portal pressure (mm. Hg)			Systemic blood-pressure (mm. Hg)		
	Method	Before vasopressin	After vasopressin	Before	During vasopressin	After
1	I.S.P.	25	15	120/90	170/110	115/85
2	I.S.P.	30	18	160/90	190/100	165/90
3	W.H.V.P.	26	16	170/95	200/100	160/90
4	I.S.P.	21	11	110/65	150/80	115/70
5	I.S.P.	31	16	130/70	170/90	120/60
6	..	..	..	130/70	150/80	135/70
7	I.S.P.	23	14	120/60	150/80	125/60
8	W.H.V.P.	25	12	140/60	150/70	140/65
Mean ..		26	14·5			
S.D. ..		3·6	3·8			

Systemic blood-pressure is given before, during, and 15 minutes after the infusion.
S.D. = standard deviation.
I.S.P. = intrasplenic pressure (normal 8–14 mm. Hg).
W.H.V.P. = wedged hepatic-vein pressure (normal 6–12 mm. Hg).

view of the small gastric remnant it was felt that a Sengstaken tube would not be tolerated and, as bleeding continued, 20 units of vasopressin was given over ten minutes. Her systemic blood-pressure was maintained at 120/60 during this period and rose to 150/80 for two minutes during the infusion. Side-effects consisted only of evacuation of the bowels. Twenty minutes after commencing vasopressin her intrasplenic pressure had fallen from a pre-treatment value of 23 mm. Hg to 14 mm. Hg. Systemic blood-pressure remained constant at 125/65. Bleeding ceased and within one hour gastric aspirates were clear of fresh blood. Four hours later blood was again aspirated, a further 20 units of vasopressin was administered and bleeding ceased for eight hours. In the subsequent twenty-four hours she bled on four occasions and each time vasopressin temporarily controlled the bleeding. She then remained free of hæmorrhage for five days and her conscious level rose from coma so that she was able to converse and take glucose drinks by mouth. She became deeply icteric, however, the serum-bilirubin reaching 40 mg. per 100 ml. Another large hæmatemesis temporarily ceased with a vasopressin infusion and blood-transfusion, but four hours later she experienced a further massive hæmorrhage and died two hours later in coma.

Postmortem revealed a finely nodular, fatty cirrhosis and œsophageal varices. The liver, gut, and heart showed no recent ischæmic changes. The gastric neoplasm had not recurred.

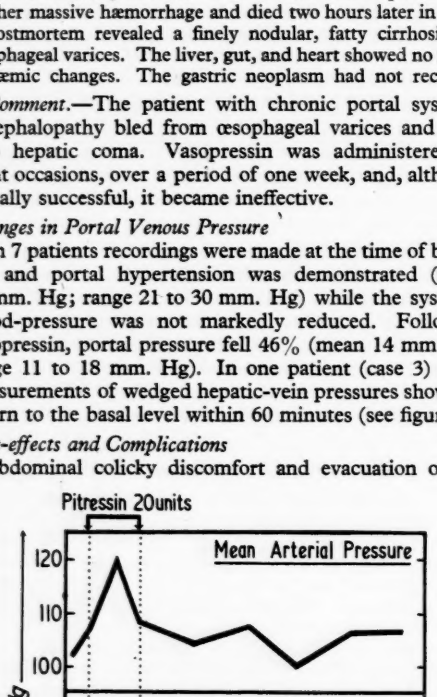
Comment.—The patient with chronic portal systemic encephalopathy bled from œsophageal varices and went into hepatic coma. Vasopressin was administered on eight occasions, over a period of one week, and, although initially successful, it became ineffective.

Changes in Portal Venous Pressure

In 7 patients recordings were made at the time of bleeding and portal hypertension was demonstrated (mean 26 mm. Hg; range 21 to 30 mm. Hg) while the systemic blood-pressure was not markedly reduced. Following vasopressin, portal pressure fell 46% (mean 14 mm. Hg; range 11 to 18 mm. Hg). In one patient (case 3) serial measurements of wedged hepatic-vein pressures showed a return to the basal level within 60 minutes (see figure).

Side-effects and Complications

Abdominal colicky discomfort and evacuation of the bowels were usual during the vasopressin infusion. In 4 patients marked facial pallor was associated with a sensation of tightness in the skin and vomiting. These effects passed off within thirty minutes. Continuous E.C.G. recordings were taken on two occasions while the vasopressin was being infused and the tracing showed no remarkable change.



Case 3: Effect of 20 units of ('Pitressin') intravenously over 10 minutes on wedged hepatic-vein pressure, mean arterial pressure, and gastric aspirations.

Postmortem examination in 5 cases revealed no ischæmic changes in the bowel, liver, or heart. 3 of these patients had received four courses of vasopressin in the twenty-four hours before death, and all had received vasopressin in the preceding fortnight.

Discussion

Posterior pituitary extract is known to lower the portal venous pressure in animals (Clark 1928, McMichael 1932, Katz and Rodbard 1939), and we have shown that this is also true in man. This effect has also been noted in 7 cirrhotic patients at operation by Schwartz et al. (1959) and in 1 cirrhotic and 1 non-cirrhotic subject, using the intrasplenic technique of portal pressure measurement by Davis et al. (1957). The mode of action in animals is attributed to constriction of the splanchnic arteriolar bed causing an increase in resistance to inflow of blood into the gut. More detailed studies of splanchnic hæmodynamics, to be published elsewhere, have confirmed this suggestion, for there is evidence of constriction of both mesenteric and hepatic arterioles and of a reduction in hepatic blood-flow (Shaldon et al. 1960). This constrictor effect on the small muscle of arterioles is generalised and the rather large dose of vasopressin used carries with it the risk of ischæmic changes developing in myocardium, liver, intestines, and elsewhere. A preliminary E.C.G. was taken in all our patients and although ischæmic changes were not noted in the 2 patients studied serially any history of coronary disease should contraindicate this therapy. Evidence of ischæmic changes in other organs was not in fact seen in the 5 patients who came to necropsy. The reduction of blood-flow through the hepatic artery after pitressin administration is of course undesirable. This is particularly so in the cirrhotic patient with a large portal collateral circulation who is depending particularly on the arterial supply to the liver. Trials of alternative methods of reducing portal pressure are continuing. Some drugs such as hexamethonium have the disadvantage of not only lowering portal blood-pressure but also systemic blood-pressure, and others such as noradrenaline do not cause a fall in portal blood-pressure as the increased resistance to splanchnic inflow is compensated by the coincident rise in systemic blood-pressure (Bearn et al. 1951, Reynolds et al. 1953, Shaldon et al. 1960).

Vasopressin has been used to control pulmonary hæmorrhage (Trimble and Wood 1950). Kehne et al. (1956) used it successfully in 2 patients with bleeding œsophageal varices and Schwartz et al. (1959) in 9 others. Both groups noted a diminished response to repeated infusions and that intramuscular vasopressin was ineffective. We have also noted that increasing the dose does not cause a greater fall in portal pressure but reducing the dose to 10 units produces a less marked effect; intramuscular vasopressin tannate is without effect. Cessation of hæmorrhage presumably results from the temporary reduction in portal pressure, allowing hæmostasis at the bleeding-point. Re-bleeding, however, is not uncommon and in the patient with liver failure this is to be expected in view of deficiencies in blood-clotting. Recurrent hæmorrhage was also seen commonly in the poor-risk patient treated with

œsophageal tamponade (Read et al. 1960) and the ultimate failure of vasopressin to control terminal hæmorrhage in this group reflects the degree of liver failure rather than the method of treatment. The value of vasopressin lies in its simplicity of use, and as an alternative to œsophageal tamponade it has many advantages. The short duration of action is obviously unsatisfactory and the side-effects from a dosage of 20 units intravenously over ten minutes are unpleasant even if short-lived. However, this dosage is necessary to achieve an adequate reduction in portal pressure, and in view of the absence of ischæmic changes following repeated administration at four-hourly intervals, its use at this level would appear to be safe.

Summary

20 units of vasopressin given intravenously in ten minutes controlled hæmorrhage from œsophageal varices in 8 patients with hepatic cirrhosis. Estimated portal pressures fell. In 3 patients bleeding did not recur, and in 2 of these portacaval anastomosis was later performed. Hæmorrhage recurred in 5 patients and a diminished response to vasopressin was observed. 4 patients died with a terminal massive bleed. The high mortality reflected the degree of liver failure rather than the method of treatment. No adverse side-effects were observed with vasopressin and its use as an alternative to the Sengstaken œsophageal compression tube is suggested.

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REFERENCES

Atkinson, M., Sherlock, S. (1954) *Lancet*, i, 1325.
Bearn, A. G., Billing, B., Sherlock, S. (1951) *J. Physiol.* **115**, 430.
Clark, J. A. (1928) *ibid.* **66**, 274.
Davis, W. D., Gorlin, R., Reichman, S., Storaasli, J. P. (1957) *New Engl. J. Med.* **256**, 108.
Katz, L. N., Rodbard, S. (1939) *J. Pharmacol. exp. Therap.* **67**, 407.
Kehne, J. H., Hughes, F. A., Gompertz, M. L. (1956) *Surgery*, **39**, 917.
McMichael, J. (1932) *J. Physiol.* **75**, 241.
Myers, J. D., Taylor, W. J. (1951) *J. clin. Invest.* **30**, 662.
Paton, A., Reynolds, T. B., Sherlock, S. (1953) *Lancet*, i, 918.
Read, A. E., Dawson, A. M., Kerr, D. N. S., Turner, M. D., Sherlock, S. (1960) *Brit. med. J.* i, 227.
Reynolds, T. B., Paton, A., Freeman, M., Howard, F., Sherlock, S. (1953) *J. clin. Invest.* **32**, 793.
— Redeker, A. G., Geller, H. M. (1957) *Amer. J. Med.* **22**, 341.
Ruskin, A. (1947) *Amer. Heart J.* **34**, 569.
Schwartz, S. I., Bales, H. W., Emerson, G. L., Mahoney, E. B. (1959) *Surgery*, **45**, 72.
Sengstaken, R. W., Blakemore, A. H. (1950) *Ann. Surg.* **131**, 781.
Shaldon, S., Dolle, W., Iber, F. L., Guevara, L., Sherlock, S. (1960) In preparation.
Sherlock, S., Summerskill, W. H. J., Dawson, A. M. (1956) *Lancet*, ii, 689.
Summerskill, W. H. J., Davidson, E. A., Sherlock, S., Steiner, R. E. (1956) *Quart. J. Med.* **25**, 245.
Taylor, W. J., Myers, J. D. (1956) *Circulation*, **13**, 368.
Trimble, H. G., Wood, H. R. (1950) *Dis. Chest*, **18**, 345.

CEREBELLAR SYNDROME IN MYXŒDEMA

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A FEW years ago a woman was fully investigated in a neurological unit on account of a cerebellar syndrome. Shortly before her discharge she was examined by a visiting colleague who promptly and originally diagnosed myxœdema. This paper is intended less as an apologia for this inability to see the wood for the trees than as a presentation of a probably not uncommon clinical entity. Six cases will be recorded as they emerged after hypothyroidism had been established.

Case-reports

Case 1 was this woman with a gross cerebellar syndrome. She was of gipsy extraction, and at the time of admission to the Churchill Hospital, Oxford, in 1954 she was 56 years old and had probably been hypothyroid for 13 years. Her gait had been unsteady for 12 years and her speech slurred for 10, and she had certainly had a sufficiently severe tremor to spill cups of tea for 3 years; she had been forced to stop work as a cook 3 months earlier and had been bed-bound for 10 weeks because of inability to stand.

In retrospect she had a typical myxœdema appearance. Her voice was almost unintelligible, and she had severe ataxia and intention tremor (left more than right) and dysdiadochokinesis, and could take only a few shuffling steps, even with very heavy assistance. Otherwise there was no abnormality in the central nervous system.

Investigations showed a serum-cholesterol of 178 mg. per 100 ml., and a cerebrospinal-fluid (C.S.F.) protein of 150 mg. per 100 ml. Two electroencephalograms (E.E.G.s) produced almost flat tracings; a lumbar air encephalogram showed a normal ventricular system but excess of cortical air, and a vertebral angiogram under general anæsthesia failed to show any abnormality. The basal metabolic rate (B.M.R.) was −30%.

Throughout her stay in hospital the patient ran a subnormal temperature and a slow pulse. She tolerated the special investigations poorly and there was delayed recovery after the anæsthetic.

Thyroid treatment was started a few days before transfer back to her local hospital. $4^1/_2$ years later she had no hypothyroid symptoms on $1^1/_2$ gr. thyroid daily. She did her own shopping but was still tremulous enough to spill cups, and her memory was poor.

On examination her speech was still slurred but intelligible. There was some titubation, and she had moderately severe tremor of the upper limbs at rest with intention tremor. She could walk steadily on a wide base only.

Thus the patient presented with an incapacitating cerebellar disorder which regressed to a moderately severe one on control of her myxœdema.

Case 2 was a 54-year-old woman in whom one of us (R. E. K.) found signs of a midline cerebellar lesion in his outpatient clinic. On admission to Maida Vale Hospital in February, 1959, she complained of 4 months of unsteadiness, coldness, and lassitude, and of 1 month of inability to walk straight and worsening handwriting.

On examination she was slow and had moderate features of myxœdema; blood-pressure 130/80 mm. Hg. She was hoarse and dysarthric and had fine nystagmus to the left, slight cerebellar ataxia in both upper limbs, and moderate trunk ataxia and a very ataxic gait.

The relevant investigations were: serum-cholesterol 360 mg. per 100 ml., greatly diminished radio-iodine uptake, C.S.F. protein 56 mg. per 100 ml., and general slowing of the E.E.G. waves. The patient was started on thyroid and lost most of her symptoms and signs within 10 days. After a month there were no abnormal signs on examination, and she has remained well on gr. 2 thyroid daily—that is, a complete remission of a moderately severe cerebellar syndrome.

Case 3 was aged 52 when she was referred to the neurological outpatient clinic at the Middlesex Hospital in February, 1952, by her general practitioner, who wrote: " For the past 6 weeks this patient has found that she falls about; she trips up; there is slurring of speech. Is this a case of D.S. ? "

She had nystagmus and bilateral ataxia and was admitted in March, 1952. It was then noted that she looked myxœdematous and had probably been so most of the previous winter. The relevant investigations were: B.M.R. −35%, serum-cholesterol 630 mg. per 100 ml., and a slow low-voltage E.E.G. tracing.

The patient was started on thyroid and improved greatly but still had slight left-sided cerebellar signs in December, 1952, when she was taking gr. $^3/_4$ a day. She continued thyroid fitfully under the care of her general practitioner, and reattended Dr. Michael Kremer's clinic in March, 1958, when she complained of general myxœdematous symptoms as well as of unsteady balance and difficulty in walking straight and a

tendency to stagger to the left. She had ptosis, nystagmus, and a slight cerebellar disorder in the left upper limb and in both lower limbs. She was found to have a greatly reduced radio-iodine uptake. Her dosage of thyroid was increased to gr. $2^1/_2$ a day and she has since remained well. In August, 1959, she had no cerebellar signs apart from minimal nystagmus on eversion to the left.

This patient therefore had a moderately severe cerebellar syndrome which remitted almost completely on thyroid but recurred 6 years later only to remit entirely when the dose of thyroid was increased to correct the hypothyroidsim.

Case 4 is a 70-year-old woman who is known to have had myxœdema since 1947, and who has had cyanocobalamin 100 μg. fortnightly since 1952 for pernicious anæmia. Since 1956 she had complained of unsteadiness and was referred to Dr. Macdonald Critchley as an outpatient in May, 1959, as she had fractured both wrists and a shoulder in four recent heavy falls.

Her ataxia was investigated while she was an inpatient in King's College Hospital in May–June, 1959. Her cholesterol was 420 mg. per 100 ml., B.M.R. −46%, radio-iodine uptake in the hypothyroid range. She was not given thyroid as she had severe effort angina. At present she has slight ataxia of the legs, and her gait is sufficiently unsteady to prevent her going outdoors without assistance.

This, then, is a relatively mild cerebellar syndrome which came on at least 7 years after the myxœdema, and which has not progressed despite lack of thyroid therapy.

Case 5 is a woman all of whose symptoms rapidly developed when she was aged 75. She remained well until November, 1957, when she suddenly felt helpless and unwell in the street; next day she noticed some unsteadiness and this progressed to its maximum within a week. The next 5 months of the winter were spent at home owing to her inability to stand or walk without support, and in this period she became hoarse and sensitive to cold for the first time in her life. 9 weeks after the onset she was seen by a neurologist and a neuro-otologist, who noted that the unsteadiness of stance and gait was worse with the eyes closed despite normal position sense, and concluded after audiometric and caloric tests that the persistent ataxia of gait was not labyrinthine in origin, but probably originated in the brain-stem. 7 months after the onset (June, 1958) the patient first saw Dr. K. W. G. G. Heathfield at St. Bartholomew's Hospital on account of the unsteadiness of her gait: he found signs of cerebellar ataxia and a suspicion of myxœdema; this was confirmed by a serum-cholesterol of 885 mg. per 100 ml. and a serum-protein-bound iodine of 0·6 μg. per 100 ml. Physiotherapy, started in July, 1958, led to a little improvement; thyroid medication was added on Aug. 15, 1958. On Sept. 5, 1958 she reported herself as being less giddy; on Sept. 28 she was walking well, and on Oct. 30 the physiotherapist reported that she could now walk without a stick. On Jan. 5, 1960, aged 77, and 2 years after the onset of symptoms, she still complained of some unsteadiness but could go for walks without a stick.

On examination she was slightly unsteady if she turned suddenly but could walk heel-to-toe and stand on one leg unsupported. She is fit on gr. 4 thyroid daily.

This cerebellar disorder seemed to come on subacutely within a week at the same time as the myxœdema and recovered completely with thyroid medication.

Case 6 is a man of 62 years who was referred to a general physician with 18 months' history of headaches, slowing, and cerebellar symptoms. His speech first became slurred and he could no longer use the telephone. Then he started to walk "like a drunken man", his handwriting deteriorated, and he had to give up his work as a designer of prestressed concrete. He was admitted to a general medical bed at St. Thomas's Hospital for investigation. On direct questioning he declared a life-long preference for hot weather but hypothyroidism was never suspected on clinical grounds.

He was seen in consultation by R. E. K., who found severe cerebellar dysarthria, moderately severe ataxia of gait, and a slight cerebellar disorder of the right upper limb. A lumbar air encephalogram showed no abnormality, the C.S.F. contained 40 and 80 mg. of protein per 100 ml. on two separate occasions. In view of our experience with the other cases in this series tests of thyroid function were carried out: the B.M.R. was −10%; and the radio-iodine uptake was low, bordering on the hypothyroid range. He was discharged on gr. 1 thyroid daily, and the dose was increased during the next month to gr. 2.

6 weeks after discharge he declared himself very much better, cured of his headaches, faster in all his activities. His gait had become normal except for occasional slight unsteadiness on turning, but he still had a moderately severe dysarthria and his handwriting remained poor.

This man with unsuspected hypothyroidism had a moderately severe cerebellar disorder which remitted partially on treatment.

Discussion

The older literature seems far more informative about this picture, probably because of the absence of a cure at that time.

White (1884) reported the case of a 56-year-old woman who was admitted to the Kent Lunatic Asylum in 1880 in a delusional state with signs of myxœdema. 4 years later she had become grossly myxœdematous; in addition to a perfect account of the general appearance, White writes as follows:

> "The muscles retain their power . . . the gait is somewhat tottering and the movements seem to lack coordination. Speech is slow and measured and very correct." He continues: ". . . the nerve force is only diminished in quantity and in the rate of its discharge"—an accurate forecast of the E.E.G. changes in myxœdema.

When in 1888 the myxœdema committee of the Clinical Society of London compiled its classical report, 39 out of 109 reported cases were found to have had some unsteadiness.

Söderbergh, of Lund in Sweden, first drew attention to the cerebellar symptoms of myxœdema by reporting two cases (1910, 1911) in which the patients lost their asynergia, adiadiochokinesis, and tremor after 2 and 5 weeks' treatment with thyroid. In 1912 Söderbergh reported three further cases—one with a clear cerebellar disorder, one dubious case, and one where the patient died in coma without much clinical detail but with the interesting, if tantalising, necropsy report that there seemed to be atrophy of the cerebellar cortex and a glistening and gelatinous appearance of the cut surface of the vermis. No microscopic findings were recorded.

A further nine cases were reported by four associates of Söderbergh (Barkman 1929, Eckerstrom 1936, Lundberg 1925, Odin 1915). Seven out of the eight uncomplicated Swedish cases recovered completely.

The lack of such case-reports in this country probably does less than justice to the true incidence of the syndrome, and lesser degrees of the syndrome may be even commoner.

All workers seem to agree that patients with myxœdema are generally rather clumsy; and Wayne (1960) regards slowness and clumsiness of movement as a valuable sign. A case of ours who was admitted to St. Thomas's Hospital with "myxœdematous madness" complained of loss of balance and of memory, and she had paranoid delusions—"someone continually trips me up". In a retrospective review of the sixty cases of myxœdema admitted to St. Thomas's Hospital in 1957 and 1958 we found recorded complaints of unsteadiness in seven.

This clumsiness and unsteadiness may well be a physical manifestation of retardation and mental lethargy. However, the symptoms and signs which we have described in the present series could not be so regarded as they were characteristically and unequivocally those of a specific

cerebellar disorder, and in none of our cases was there evidence of sufficient retardation to explain the signs. Indeed, the implication cannot be avoided that the many cases in which slowness and clumsiness have been observed and accepted as part of the picture of myxœdema were in reality demonstrating the earlier signs of the syndrome we are discussing here.

Three further possible contributory factors need to be considered when seeking an explanation of unsteadiness in myxœdema. Firstly, myxœdematous infiltration of tongue, lips, fingers, &c.: this was notable only in our first case, and she was left with a moderate cerebellar dysarthria long after having lost her myxœdema. Secondly, peripheral neuropathy is known to occur (Crevasse and Logue 1959); there was none in our six cases. Thirdly, labyrinthine disorders are associated with myxœdematous deafness (Clinical Society of London 1888, Moehlig 1927); none of our cases had true vertigo and significant vestibular disorders were excluded in the fourth and fifth cases by a neuro-otologist.

One would wish to include in a discussion of the syndrome the reported neuropathological changes of myxœdema, but there are few clear-cut accounts of the changes in the brain and none of the changes in the cerebellum that we have been able to find, so one has to fall back on the clinical picture.

The progress in our cases has ranged from 1 week to 12 years and seems to fluctuate: the disability often seems less after admission to hospital than before. In our five treated cases it remitted within 2–8 weeks of starting thyroid (completely in two), but our first case was left with an appreciable cerebellar disorder. One is therefore tempted to postulate metabolic or vascular processes which may lead to degeneration.

In contrast, the subacute cerebellar degeneration of malignant disease reported by Brain et al. (1951) does not seem to remit. But one should perhaps recall the capacity of the central nervous system to recover from—or, perhaps, compensate for—non-progressive cerebellar lesions; for instance, the recovery of function after simple surgical lesions.

The diagnosis hinges on the awareness of the clinician, although in our second and sixth cases the features of myxœdema were by no means obvious: three of these cases had been through the hands of general physicians who had failed to recognise the myxœdema.

Special investigations have been reviewed recently by Wayne (1960). Our first and most severe case had a serum-cholesterol of only 178 mg. per 100 ml.

Conclusion

In conclusion we wish to draw attention to the existence of a cerebellar disorder in myxœdema. We wish to stress that hypothyroidism should be considered and excluded in obscure cerebellar pictures; that the myxœdema may not be at all obvious, and has been missed even when it is; and that this is a treatable neurological syndrome. Five out of the six cases reported here were treated with thyroid, and the cerebellar syndrome remitted promptly on every occasion within a few weeks.

And lastly, a quotation: " A skilled anatomist should dissect their brain and should see whether their cerebellum has fewer convolutions and less deep fissures "—a call for a neuropathological study which is no less apposite for having been written in 1786 by de Saussure about the cretins of the Swiss Alps.

Summary

Six cases of myxœdema are described which presented with moderate to severe cerebellar syndromes. The cerebellar signs remitted promptly with thyroid medication in the five cases treated thus.

We wish to record our thanks to Dr. Laurence Newborne, of Newbury, for diagnosing myxœdema in the first case; to Dr. W. Ritchie Russell, Dr. Michael Kremer, Dr. Macdonald Critchley, Dr. K. W. G. G. Heathfield, and Dr. Evan Jones for allowing us to publish the first, third, fourth, fifth, and sixth cases respectively; and to Dr. M. L. E. Espir, Dr. N. S. C. Gent, Dr. R. E. Lovelace, and Dr. R. G. Willison for their help in tracing three of these cases.

REFERENCES

Barkman, A. (1929) *Acta med. scand.* **71,** 479.
Brain, W. R., Daniel, P. M., Greenfield, J. G. (1951) *J. Neurol. Neurosurg. Psychiat.* **14,** 59.
Clinical Society of London (1888) Report of myxoedema committee.
Crevasse, L. E., Logue, R. B. (1959) *Ann. intern. Med.* **50,** 1433.
de Saussure, H. (1786) Voyages dans les Alpes; vol. 4, p. 291.
Eckerstrom, S. (1936) *Acta med. scand.* **90,** 207.
Lundberg, R. (1925) *ibid.* **16,** suppl. p. 182.
Moehlig, R. C. (1927) *Endocrinology,* **11,** 229.
Odin, M. (1915) *Hygeia, Stockh.* **77,** 289.
Söderbergh, G. (1910) *Rev. neurol.* **20,** 487.
— (1911) *ibid.* **22,** 86.
— (1912) *Nord. med. Ark.* **45,** no. 11. p. 1.
Wayne, E. J. (1960) *Brit. med. J.* i, 78.
White, E. W. (1884) *Lancet,* i, 974.

VALUE OF A LARGE DOSE OF ANTITOXIN IN CLINICAL TETANUS

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IT may be considered a reproach to modern medicine that in 1955 it was possible for two authorities on bacteriology to write: " Whether or not antitoxin is of any value in man given subsequently to the development of tetanus is a question that has received no definite answer " (Wilson and Miles 1955). Studies in animals have demonstrated that antitoxin can be of value in this circumstance, but there is not agreement on just how valuable.

Most animal experiments have been performed using injected tetanus toxin and are more remote from the conditions of the clinical disease than the minority done by infecting animals with tetanus spores. A recent study using the latter method (Turner et al. 1958) suggests that antitoxin may prolong life rather than prevent death —an opinion which accords with the experience of Tompkins (1958) in human neonatal tetanus.

While physicians have long been completely convinced of the great efficacy of antitoxin in *preventing* tetanus,

many are unimpressed by its ability to preserve life once symptoms of the disease have appeared (Bruce 1920, Creech et al. 1957, Huntington et al. 1937, Johnstone 1958, Tompkins 1958). We have been unable to find a clinical report which supports the efficacy of antitoxin in treatment of the developed disease and which also reaches modern criteria of satisfactory evidence of therapeutic effect. Despite this there is a reasonable presumption that antitoxin should be used; for, although toxin already in the central nervous system cannot be neutralised, there is also for a time toxin in the blood, lymph, and tissues which may be neutralised by antitoxin given promptly, and so prevented from reaching the central nervous system. If this toxin can be neutralised early and the bacterial source of toxin destroyed by chemotherapy, it may be possible to prevent a fatal amount of toxin reaching the central nervous system. The hope of achieving this has rendered the use of antitoxin orthodox practice despite the lack of evidence that it is beneficial.

If the injection of tetanus antitoxin were a trouble-free procedure one might hesitate before undertaking a controlled therapeutic trial in the face of the theoretical presumption in its favour, which receives some support from animal experiments. But not only is the practical value of antitoxin in doubt, but its administration is troublesome and sometimes hazardous even to the point of causing death. Furthermore, antitoxin is expensive.

The knowledge that there are hospitals in India (Vakil 1960) and in Africa, where tetanus is common, in which tetanus antitoxin is not used in all cases, both because the worth of this remedy is considered unproved and because money for supplies is not always to be had, prompted us to attempt to obtain a clear answer to the following question: does the mortality-rate of patients with tetanus receiving a large dose of antitoxin differ from that of those receiving none? The dose chosen for adults was 200,000 I.U. tetanus antitoxin.

Method

This investigation was conducted jointly between London, Ibadan, and Jamaica. The design and analysis were done in London and the patients were treated in Ibadan and Jamaica.

The basic principles of the trial were: (*a*) that all treatment should be identical within each centre, with the exception of the administration of antitoxin; (*b*) that the two groups of patients should as far as possible be equivalent in all relevant respects. The latter requirement could best be met by allotting the patients to receive antitoxin or not at random, although, as is pointed out below, in this trial a rather higher proportion of severely ill patients happened to be allocated to the group receiving no antitoxin than to that receiving antitoxin. It was not possible to divide the patients initially into strata of differing severity and to arrange that the two treatments were represented equally in each stratum since the choice of treatment had to be decided immediately the patient presented at hospital.

It was obvious that both treatments must be conducted concurrently to eliminate variables such as changing medical and nursing staff, climate, and variations in potency of antitoxin, which might influence the outcome of the disease.

The salient features of the trial were as follows:

(1) All patients other than neonates who were diagnosed as having tetanus were admitted to the trial.

(2) Patients were allotted to their treatment group after diagnosis by opening the next of a previously prepared series of envelopes containing randomised allocations indicating whether the patient was to receive antitoxin or not.

(3) Patients who were to receive antitoxin had 200,000 I.U. on admission to hospital if they were over 10 years old. A total of 100,000 I.U. was given to patients under 10 years old. Details of route varied slightly in the different centres (all was given intramuscularly at Ibadan and half intramuscularly and half intravenously in Jamaica) but were consistent within each centre. Patients were tested for sensitivity to horse-serum prior to administration, and in the event there were no serious serum reactions.

(4) Anticonvulsant treatment was based on a combination of chlorpromazine and barbiturates as advocated by Adams et al. (1959), but variation was permissible between centres provided treatment remained consistent within the centres. Neuromuscular blocking-agents were not used.

(5) All patients received standard doses of penicillin, chiefly to kill the tetanus organisms, and other antimicrobials as clinical judgment indicated.

(6) Wounds were treated as they would have been in the absence of tetanus.

(7) Feeding and nursing procedures conformed to accepted practice in the disease, being conducted as far as possible when sedation was at its height.

(8) Tracheostomy was performed if the physician in charge considered it essential.

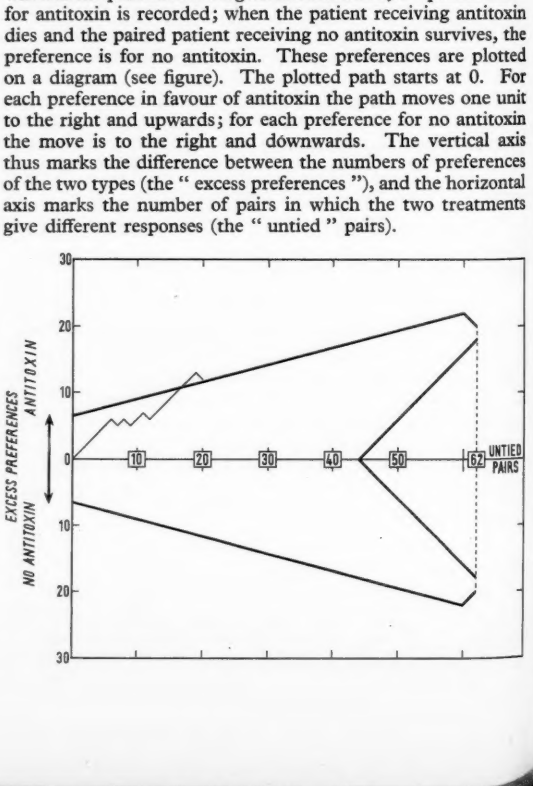
(9) Standard forms for each patient were filled in. They recorded a range of information to be used in the analysis. On completion these were sent to London.

Sequential Analysis

The use of sequential analysis in medical trials is described by Armitage (1960). In a sequential analysis the observations are examined as they become available, and the decision whether to stop a trial at any stage depends on the results so far obtained. If these results indicate a notable difference between the responses in different treatment groups, the trial will finish quickly. The main question in the present trial was whether mortality was affected by the use of a high dose of antitoxin; and, if at any stage this question could be confidently answered, it would obviously be unethical to continue the trial to provide answers to subsidiary questions.

The method used was as follows. Successive patients allocated to the two treatments were regarded as paired (i.e., the first patient receiving antitoxin was paired with the first receiving no antitoxin, and so on). The random allocation was so arranged that in each centre the numbers allocated to the two groups were balanced after each 10. The pairing was, however, performed in the order in which the record cards were received by the statistician.

If, for any pair, the patient receiving antitoxin survives whereas the patient receiving no antitoxin dies, a " preference " for antitoxin is recorded; when the patient receiving antitoxin dies and the paired patient receiving no antitoxin survives, the preference is for no antitoxin. These preferences are plotted on a diagram (see figure). The plotted path starts at 0. For each preference in favour of antitoxin the path moves one unit to the right and upwards; for each preference for no antitoxin the move is to the right and downwards. The vertical axis thus marks the difference between the numbers of preferences of the two types (the " excess preferences "), and the horizontal axis marks the number of pairs in which the two treatments give different responses (the " untied " pairs).



The trial stops when one of the boundaries is reached. The divergent lines forming the upper and lower boundaries represent significant differences betwen the two treatments. The middle, wedge-shaped, boundary represents a non-significant difference. The upper and lower boundaries have been chosen so that, if antitoxin were ineffective, each boundary would be reached about once in 40 times (Armitage 1960, table III, 7). These two boundaries thus correspond to a 1 in 20 (5%) significance level. If, on the other hand, antitoxin is so effective that, in the long run, say, 75% of the preferences favour antitoxin, there are 19 chances out of 20 (i.e., a probability of 95%) that the upper boundary will be reached—i.e., that the difference will be detected. This preponderance in favour of antitoxin would happen if, for example, the proportion of deaths was 50% with antitoxin and 75% without antitoxin.

The maximum number of preferences needed before the trial ends is 62 (see figure). Since rather less than half the pairs of patients were likely to provide preferences, the number of patients required would be at the most about 150 in each treatment group.

TABLE I—DATA ON TREATMENT GROUPS

—	*Antitoxin*	*No antitoxin*
No. of cases:		
Nigeria	35	32
West Indies	6 } 41	6 } 38
Mean age (yr.)	24·8	27·1
Race:		
Ibadan—African	35	32
West Indies—Negro	5 } 41	3 } 38
Others	1	3
Sex:		
Male	23 } 41	21 } 38
Female	18	17
Mean incubation period (days)	10·1 (26 cases)	9·7 (29 cases)
Mean period of onset (days)	3·0 (33 cases)	3·2 (34 cases)
Intercurrent disease or complications:		
None	18	15
Pulmonary infection	5	10
Hyperpyrexia	6	7
Laryngospasm	1	2
Postpartum	6	5
Miscellaneous	12	6
Severity on admission:		
Local	0	2*
General—mild	9 } 41	4 } 38
moderate	12	9
severe	20	23
Site of wound:		
Limbs	22	22
Head and neck	1	1
Trunk	1 } 41	1 } 38
Genital tract	6	5
Not known	11	9
Sepsis (excluding postpartum cases):		
Present	10 } 35	8 } 33
Absent	25	25

* 1 became generalised and 1 remained confined to the head and neck.

Comparability of Treatment Groups

Table I shows that the two treatment groups are similarly constituted with respect to various criteria. The most important complications which might influence the outcome are recorded. Miscellaneous complications included hepatitis, worm infestation, arterial thrombosis in limbs, sickle-cell anæmia, diabetes, and tuberculosis. 3 patients had tracheostomy (2 without antitoxin).

Records were inevitably incomplete for two of the principal prognostic factors—period of onset as defined by Cole (1940) and incubation period. To provide as complete a classification as possible for these two factors, the patients were classified by the definitions, which were made before the trial started:

Prognostic group I.—Period of onset 36 hours or less. If period of onset unknown: incubation period 6 days or less.

Prognostic group II.—Period of onset more than 36 hours. If period of onset unknown: incubation period more than 6 days.

Prognostic group III.—Period of onset and incubation period both unknown.

TABLE II—PROPORTION OF DEATHS IN EACH TREATMENT GROUP

—	Antitoxin	No antitoxin
Deaths	20	29
Survivals	21	9
Total no. of cases	41	38
Proportion of deaths (%)	49	76

The distribution of patients according to these prognostic groups is given in table III. The treatment group receiving no antitoxin included a higher proportion of patients in prognostic group I—a lack of balance which would tend to favour the treatment group receiving antitoxin. This difficulty is considered below.

Results

Sequential Analysis of Mortality

The sequential path is shown in the accompanying figure. The upper boundary (in favour of antitoxin) was crossed at the 18th preference. At this stage 15 preferences were in favour of antitoxin and 3 in favour of no antitoxin. If antitoxin were really ineffective, the probability of crossing a boundary with at least as high a preponderance in favour of one of the treatments—i.e., at an even earlier stage—is less than 0·02. When the boundary was crossed, and the decision taken to stop the intake of patients into the trial, 39 patients had been treated with antitoxin and 32 without. Subsequently, records became available for 2 patients treated with antitoxin and 6 without. These additional records increased the number of preferences by 2, as is shown in the figure. The total numbers of deaths and survivals in the two treatment groups are given in table II. The proportions of deaths are 49% of the patients with antitoxin, and 76% of the patients with no antitoxin.

The question now arises whether the higher mortality in the group receiving no antitoxin is largely due to the unfavourable distribution of the prognostic grouping referred to above. Table III shows the mortality in each prognostic group for each treatment. Mortality is higher in prognostic group I than in prognostic group II; it is also higher in the treatment group receiving no antitoxin than in that receiving antitoxin, for each of the prognostic groups. For each prognostic group the difference in mortality for the two treatment groups is shown in the final column. The most striking difference is in prognostic group II. These three differences are now averaged (each being weighted in inverse proportion to its sampling variance); and the mean difference is 20%, with a standard error of 10%—a result which is just significant at the 5% level by the customary test. The trial having been performed sequentially, rather less weight should be given to this degree of significance than would otherwise be (Armitage 1960), but there is clearly a substantial degree of evidence that antitoxin reduces mortality.

Tables IV and V show the mortality in relation to the incubation period and the period of onset separately. In both these tables, the mortality in each subgroup is

TABLE III—PROPORTION OF DEATHS RELATED TO CLASSIFICATION BY PROGNOSTIC GROUPS, ACCORDING TO PERIOD OF ONSET AND INCUBATION PERIOD

Group	Antitoxin		No antitoxin		Difference in percentage deaths ±S.E.
	Deaths/total	%	Deaths/total	%	
I	15/21	71	22/26	85	14±12
II	4/18	22	6/11	55	33±18
III	1/2	50	1/1	100	50±58
	20/41		29/38		

Weighted mean difference ±S.E.: 20±10 (P=0·04).

TABLE IV—PROPORTION OF DEATHS RELATED TO INCUBATION PERIOD

Incubation period (days)	Antitoxin		No antitoxin	
	Deaths/total	%	Deaths/total	%
0–6	3/6	50	6/10	60
7–12	7/14	50	8/10	80
>12	2/6	33	8/9	89
Unknown	8/15	53	7/9	78
	20/41		29/38	

TABLE V—PROPORTION OF DEATHS RELATED TO PERIOD OF ONSET

Period of onset	Antitoxin		No antitoxin	
	Deaths/total	%	Deaths/total	%
0–36 hr.	15/21	71	20/24	83
36 hr.–	1/4	25	4/4	100
3 days–	0/10	0	1/6	17
Unknown	4/6	67	4/4	100
	20/41		29/38	

higher in patients receiving no antitoxin than in those receiving antitoxin. It is now well known that the period of onset is the more valuable prognostic index, and these tables confirm this.

Discussion

This trial was conducted because " Where the value of a treatment, new or old, is doubtful, there may be a higher moral obligation to test it critically than to continue to prescribe it year-in-year-out with the support merely of custom or of wishful thinking " (Green 1954).

It was considered whether it would be desirable to supply coded ampoules containing active and inactivated antitoxin for random administration to patients, in order to avoid any possibility of bias among clinical staff affecting the outcome of the trial if they once became convinced of the value or lack of value of antitoxin. It seemed that this could possibly take the form of unconsciously giving less care to patients who were considered to be " protected " by the antitoxin or perhaps of similarly giving up hope for patients who were " unprotected ". A " blind " technique was not used because it was thought unjustified to take risks of serum reactions in patients who were being given a deliberately inactivated serum, and because the mere act of injection can sometimes precipitate severe spasms that can endanger life, and so should only be risked if there is a possibility of some benefit. In addition it was essential to keep the trial as simple as possible, as undue complexity is a potent cause of failure of clinical trials. It was not thought that the risk of bias due to knowledge of who had had antitoxin and who had not was a very serious one.

The random allocation ensured that the two treatment groups were closely similar in many respects. There was, however, a greater proportion of patients with a poor prognosis (i.e., short period of onset or incubation period) in the group treated without antitoxin than in the antitoxin group, and it was important to see whether this lack of balance could have explained the difference in response between the two groups. The patients were classified into three prognostic groups, according to period of onset and incubation period. Within each of these groups patients treated with antitoxin showed a higher survival-rate than those without antitoxin. By contrasting the two treatment groups within each of the three prognostic groups, and then forming an average of these three contrasts, the effect of antitoxin was shown to be significant at about the 5% level. The unfavourable allocation, therefore, does not explain the general finding in favour of antitoxin.

We conclude that the administration of antitoxin is an important part of the treatment of clinical tetanus. Further clinical trials are being conducted to find the optimum dose.

The expense of using tetanus antitoxin is by no means small. 200,000 I.U. costs about £8 in Ibadan, less in Jamaica; and even since this trial was conducted there has been a period during which some patients in Ibadan received no antitoxin because there was none to give them. It seems that, beneficial though antitoxin almost undoubtedly is in tetanus, its use is likely to be impossible for some time to come in certain countries where tetanus is common.

Summary

The beneficial effect of antitoxin in clinical tetanus has not previously been established, and in many places it is not used.

A clinical trial to test the value of antitoxin has been carried out.

The mortality rate was 49% among patients receiving 200,000 I.U. of antitoxin and 76% in those not receiving antitoxin. The probability of this result arising by chance is less than 1 in 20. After correction for a chance allocation which favoured the group receiving antitoxin, there was still a substantially lower mortality among patients in this group.

Tetanus antitoxin is a valuable remedy in clinical tetanus.

We are grateful to Mr. V. K. Asta for the figure.

REFERENCES

Adams, E. B., Wright, R., Berman, E., Laurence, D. R. (1959) *Lancet*, i, 755.
Armitage, P. (1960) Sequential Medical Trials. Oxford.
Bruce, D. (1920) *J. Hyg., Camb.* **19**, 1.
Cole, L. (1940) *Lancet*, i, 164.
Creech, O., Glover, A., Ochsner, A. (1957) *Ann. Surg.* **146**, 369.
Green, F. H. K. (1954) *Lancet*, ii, 1085.
Huntington, R. W., Thompson, W. R., Gordon, H. H. (1937) *Ann. Surg.* **105**, 93.
Johnstone, D. D. (1958) *Brit. med. J.* i, 12.
Tompkins, A. B. (1958) *ibid.* p. 1382.
Turner, T. B., Velasco-Joven, E. A., Prudovsky, S. (1958) *Bull. Johns Hopk. Hosp.* **102**, 71.
Vakil, B. J. (1960) Personal communication.
Wilson, G. S., Miles, A. A. (1955) Topley and Wilson's Principles of Bacteriology and Immunity; vol. 2, p. 1971. London.

WOUND HEALING AS DEPENDENT ON RATE OF HISTAMINE FORMATION

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New approaches to the physiology of histamine became possible when methods were found of measuring the rate of histamine formation—the histamine-forming capacity (H.F.C.). This, again, was a prerequisite in evolving means of altering the H.F.C. artificially. Extensive studies of the tissue content of histamine under various conditions have added little to our understanding of the physiological role of histamine. The rate of formation and content of histamine do not run parallel, and should not be confused.

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Some tissues contain little histamine but form it at a high rate, and vice versa.

Using the new methods at this institute a connection between growth of the embryo and its H.F.C. was discovered. During a certain phase of development, the embryo of the rat and of man produces histamine at a very high rate as a result of high histidine-decarboxylase activity. Inhibiting the fœtal histamine formation arrests the growth of the embryo which then disintegrates in utero. An account of this work has already been published (Kahlson 1960).

Encouraged by the discovery of the dependence of embryonic growth on the H.F.C. of the embryo, we turned to the study of a different type of rapid growth—the reparative growth in healing skin wounds. This venture seemed promising because in the skin the H.F.C. can be artificially lowered or raised.

Methods

Wounds.—White rats of 200–250 g. body-weight were used, and two incised wounds in the skin of the back were studied in each animal. Both wounds were made under ether anæsthesia; the first, or control wound, was left to heal under normal conditions before the second or test wound was inflicted, and this wound healed under experimentally altered conditions. The wounds, which were 6 cm. long, were placed symmetrically 1·5 cm. from the midline and parallel to it. Each half of the skin of the back was shaved immediately before infliction of its wound. The incisions were made with a knife through the skin and the subcutaneous muscle layer. Ligatures were not used to stop bleeding. The wounds were closed by continuous through-and-through silk sutures, with stitches 5 mm. apart, and they were not dressed. To prevent the rats biting the sutures a padded collar of X-ray film was placed around their necks.

Index of the rate of repair.—The tensile strength (T.S.) of the healing wound in situ, generally recognised as reflecting the rate of repair, was determined 5 days after wounding by a special type of tensiometer (Sandblom et al. 1953). The T.S., defined as the force just sufficient to disrupt the wound, is expressed in grammes of pull. For each determination the sutures were removed and the T.S. of three 1 cm. lengths of the 6 cm. wound was measured. The three readings were averaged, and the mean was taken to represent the T.S. of the whole wound. There was little scatter among the individual readings. The differences in T.S. of control and test wounds are expressed as a percentage of the control value.

Determination of H.F.C. in vitro.—Granulation tissue was allowed to grow into plastic sponges ('Ivalon'), $3 \times 1 \times 0{\cdot}3$ cm. in volume, placed between the skin and underlying muscle. Wound tissue, as sampled, included 2–3 mm. of the edges of the wound, and comprised the wound tissue proper admixed with newly formed granulation tissue. The tissues were minced, suspended in phosphate buffer, and incubated with ^{14}C-histidine as originally described by Schayer (1956). The amount of ^{14}C-histamine formed was measured by isotope dilution; the procedures used have been fully reported (Kahlson, Rosengren, Westling, and White 1958, White 1959).

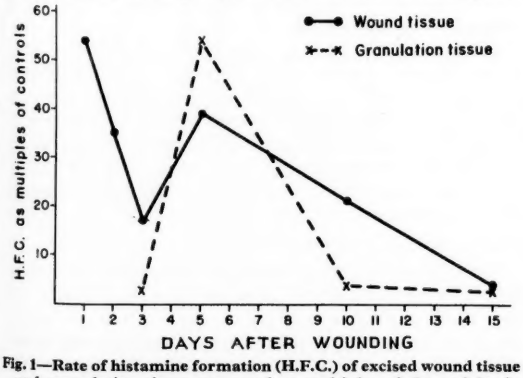

Fig. 1—Rate of histamine formation (H.F.C.) of excised wound tissue and granulation tissue expressed as multiples of the activity in whole skin from the same rat.
Each figure is the mean of determinations in two rats.

TABLE I—H.F.C. IN VITRO, EXPRESSED AS AMOUNT OF RADIOACTIVE HISTAMINE IN COUNTS PER MIN. PER G. RAT TISSUE FORMED FROM ^{14}C-HISTIDINE

Fœtal liver [1]	14,000–23,000
Stomach [2]	370– 980
Mast-cell tumour (dog) [3]	470– 530
Granulation tissue, 5th day	100– 225
Wound tissue, 1st day	140– 155
Lung [2]	90– 150
Hypothalamus (cat) [4]	90– 125
Total brain [2]	20– 35
Skin of the back	2– 10

(Figures quoted from: 1. Kahlson et al. [1960]. 2. Kahlson et al. [1958]. 3. Lindell et al. [1959]. 4. White [1959].)

Determination of H.F.C. in vivo.—Recently two approaches have been found for determining the rate of histamine formation in the whole animal. One method depends on the finding that, in the female rat fed on a histamine-free semisynthetic diet, the urinary excretion of free histamine runs parallel with the rate of endogenous histamine formation (Gustafsson, Kahlson, and Rosengren 1957). The other method, devised by Schayer et al. (1954), measures the urinary excretion of radioactive histamine after the injection of radioactive histidine. Both procedures have been used in this work.

TABLE II—HISTAMINE CONTENT (μG. BASE PER G.) IN RAT TISSUES ON THE 5TH DAY AFTER INFLICTING THE WOUND (EXTRACTS ASSAYED ON GUINEAPIG ILEUM)

Rat no.	1	2	3	4
Wound tissue	5·4	8·7	6·6	6·5
Granulation tissue	1·7	1·6	1·4	1·1
Skin of the back	16·5	13·3	20·6	18·0

Results

H.F.C. of Excised Tissue

Granulation tissue and wound tissue were obtained at various intervals after wounding, and the H.F.C. was compared with that of abdominal skin from the same rat (fig. 1). Wound tissue excised 24 hours after infliction of a wound had a high H.F.C.; the histidine-decarboxylase level was 50–60 times the level in control skin. The H.F.C. of wound tissue declined on the 2nd and 3rd days, but was high again on the 5th day coincident with the rise in H.F.C. of the granulation tissue. This was not measured during the first two days because at that time granulation tissue has not penetrated the ivalon sponges. In the granulation tissue the H.F.C. reached a peak at the 5th day and then fell steeply. The high activity seen in wound tissues at the 5th day is likely to reside mainly in the granulation component. For comparison the H.F.C. of various tissues are presented in table I.

Histamine Content of Excised Tissue

In four rats which were not given injections to alter the H.F.C., granulation tissue, wound tissue, and intact skin from the corresponding opposite region of the back—were examined for histamine at the 5th day of wounding. The H.F.C. of the reparatively growing tissues was then very high (fig. 1). Nevertheless the histamine content of these tissues was much lower than that of intact skin (table II). This applies particularly to granulation tissue of which the histamine content is lower than any other tissue of the rat so far examined. The histamine formed so rapidly is not held by these tissues. The property of high H.F.C. and

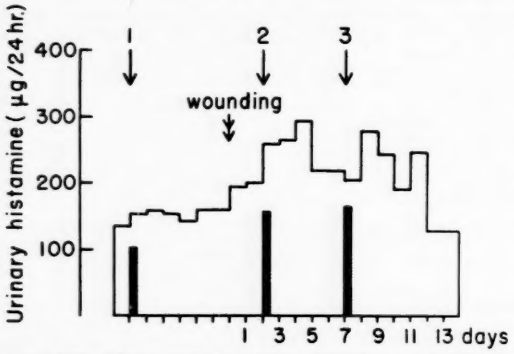

Fig. 2—Daily urinary excretion of free histamine in a female rat.
The arrows 1, 2, and 3 indicate subcutaneous injection of radioactive histidine 110 µg. and the solid vertical columns represent urinary excretion of radioactive histamine resulting from these injections. Aminoguanidine was given throughout to prevent the destruction of histamine by histaminase.

concomitant low-histamine content is characteristic also of embryonic tissues (Kahlson, Rosengren, and White 1960).

H.F.C. Examined in Vivo

To get the best results in these experiments, four incisions of standard type were made simultaneously in the skin of the back. The daily excretion of free histamine was estimated by collecting the urine and assaying it directly on a piece of guineapig gut, as described by Kahlson, Rosengren, and Westling (1958). As a further means of measuring the rate of histamine formation, radioactive histidine was injected subcutaneously, and the radioactive histamine excretion was measured. Fig. 2 shows that the urinary histamine increases on the day of wounding, reaches a peak on the 5th day, and then returns to normal on the 13th day. The changes in the rate of histamine formation, as expressed by its urinary excretion, agree well with the corresponding observations in excised tissues (fig. 1). In one rat (fig. 2) radioactive histidine 110 µg. was injected before and after wounding. Injection before wounding resulted in 700 counts per min. radioactive histamine excreted in 72 hours, and injections at the 2nd and 7th days after wounding in 1100 and 1160 counts per min. respectively. Similar results

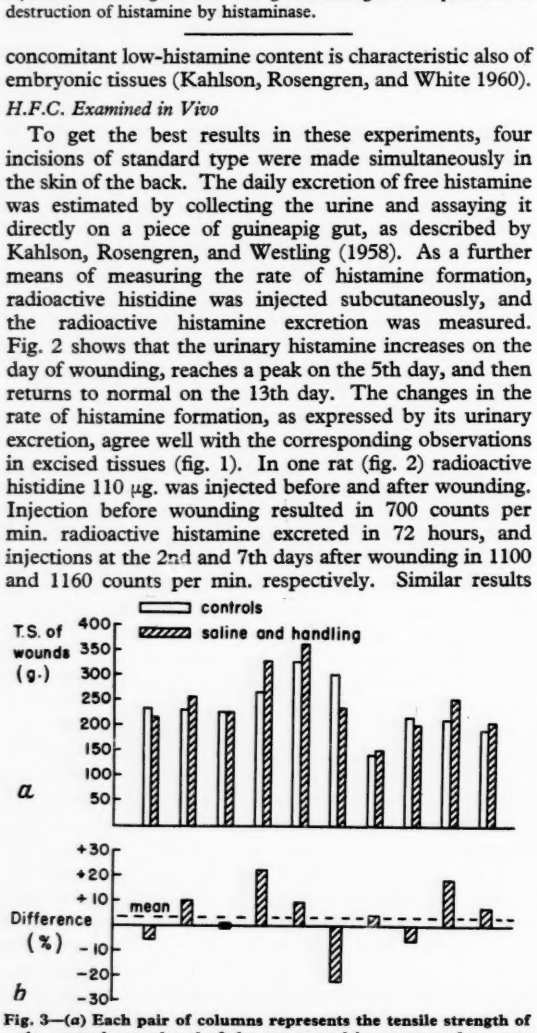

Fig. 3—(a) Each pair of columns represents the tensile strength of the control wound and of the test wound in a group of ten rats (saline, 3 ml. intraperitoneally, was injected on 3 successive days before the test wound was inflicted); in (b) the effect of this treatment on the tensile strength is expressed as difference (%) against the control.

were obtained in three other rats. These results do not imply liberation of preformed histamine, but increased formation of the amine.

Rate of Repair in Normals and Controls

Observations on ten normal rats (fig. 3) show considerable variation in the rate of normal healing. This did not affect our study because, in most animals identical wounds inflicted as described and left untreated, healed with no apparent difference in rate. Moreover healing both under normal and artificially altered conditions was observed in the same individual. In the group of ten rats the mean T.S. value for test wounds inflicted after handling and after saline injections did not differ significantly from the mean for control wounds (fig. 3).

Rate of Repair at Elevated H.F.C.

In the skin of the rat the level of histidine-decarboxylase activity can be adaptively increased under the influence of repeated injections of the histamine liberators 48/80 or polymyxin B (Schayer et al. 1959, Schayer and Ganley 1959). We have confirmed these findings.

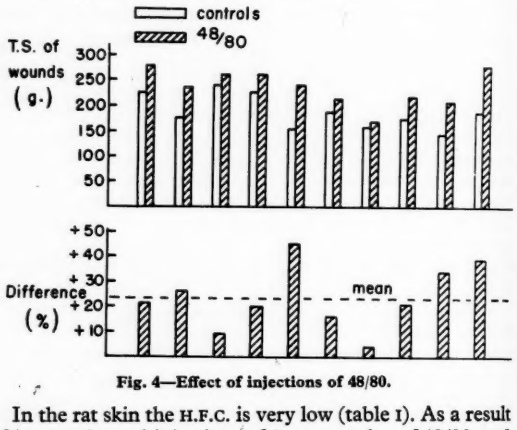

Fig. 4—Effect of injections of 48/80.

In the rat skin the H.F.C. is very low (table I). As a result of intraperitoneal injections of 1 mg. per kg. of 48/80 on 3 successive days, the H.F.C. increased to 5–6 times normal. The test wound was inflicted 24 hours after the last injection. At this stage the histamine content of the skin is reduced to a small fraction of normal, whereas the H.F.C., as a result of the adaptive increase in histidine-decarboxylase activity, is high. Observations on the rate of repair in skin subjected to such changes are presented in fig. 4; healing is significantly more rapid in the skin with an elevated H.F.C. This arises in skin depleted of the major part of its histamine store.

Polymyxin B, a more specific histamine liberator than 48/80 (which releases both histamine and 5-hydroxytryptamine), was injected into ten rats in doses of 2 mg. per kg. as in the experiments with 48/80. In addition to depleting the skin of most of its histamine content this treatment approximately doubled the amount of H.F.C. when the test wound was inflicted. The rate of healing was accelerated by a mean of 18%.

Rate of Repair at Lowered H.F.C.

A means of inhibiting histamine formation has recently been devised (Kahlson and Rosengren 1959). Feeding rats on a diet deficient in pyridoxine (thus depriving histidine decarboxylase of its coenzyme) and superimposing injections of the enzyme inhibitor semicarbazide reduced the rate of histamine formation considerably. At a stage when the H.F.C. was as low as about 20% of normal the healing

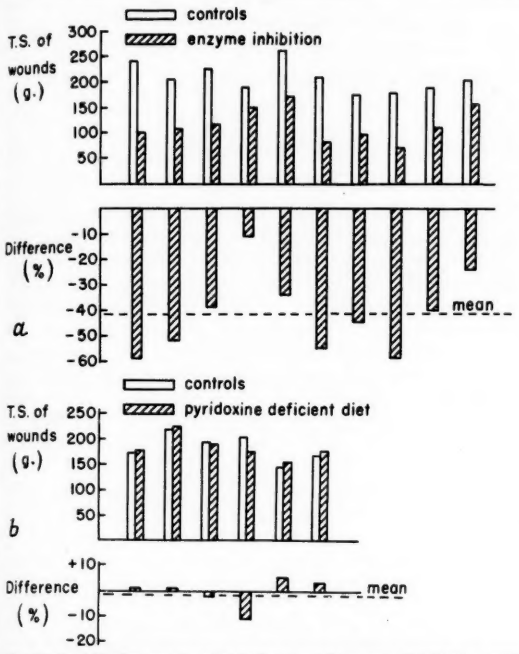

Fig. 5—(*a*) Healing under the influence of enzyme inhibition with semicarbazide superimposed on a pyridoxine-deficient diet; (*b*) the effect of the deficient diet alone.

was grossly retarded, whereas simply feeding the animals on the deficient diet for 3–4 weeks had no detectable effect on healing (fig. 5). Semicarbazide inhibits various enzymes besides histidine decarboxylase, among them other aminoacid decarboxylases.

The " Overshooting Phase "

On discontinuing semicarbazide and restoring pyridoxine to the diet, the inhibition of histamine formation ceases and is rapidly followed by an overshooting phase, which lasts for more than a week, when the rate of histamine formation increases 2–4 times. The " overshoot " seems to arise because newly formed molecules of histidine decarboxylase become active when pyridoxine is restored to the diet. This invokes the assumption that semicarbazide concomitantly inhibits the enzyme and stimulates the formation of new molecules of the enzyme (Kahlson and Rosengren 1959). Whatever the mechanism of the elevated H.F.C. in the overshooting phase, it is significant that healing is enhanced in association with the raised H.F.C. In a series of eight rats examined during the overshooting phase the mean increase in the rate of healing was 53%, as shown in fig. 6.

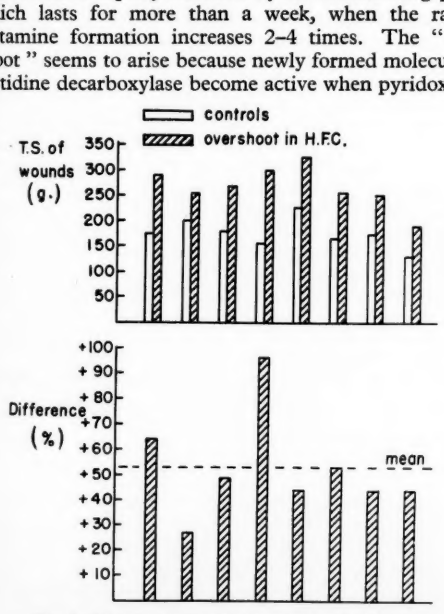

Fig. 6—Healing during the " overshooting phase ".

The Role of Extracellular Histamine

Granulation and wound tissues contain little histamine, yet they produce the amine at high rates. Histamine formed intracellularly will diffuse into the extracellular spaces, and thence enter the blood-stream to be distributed all over the body. As a result the granulation and wound tissues are exposed to extracellular histamine in considerable concentration. It may be argued that histamine, acting from outside rather than inside the cells, constitutes the effective stimulus to reparative growth. To settle this issue granulation and wound tissues were flushed by extracellular histamine derived from " long-acting histamine " deposited under the skin. An oily suspension of histamine dipicrate, which is poorly soluble in water, was injected at sites distant from the wound region in doses of 1·5 mg. (four rats) and 3·0 mg. (five rats) daily for 5 days after the test wounds were inflicted. From this depot histamine is slowly absorbed into the blood-stream, distributed over the body, and, with the doses used, excreted in the urine in daily amounts of 2–4 times the histamine excretion-rate resulting from the four wounds, as shown in fig. 2. Exposure in this manner to extracellular histamine did not influence the rate of repair (fig. 7). This finding is somewhat at variance with the histological evidence of the advanced rate of wound healing in rats given intraperitoneal injections of histamine acid phosphate (Boyd and Smith 1959).

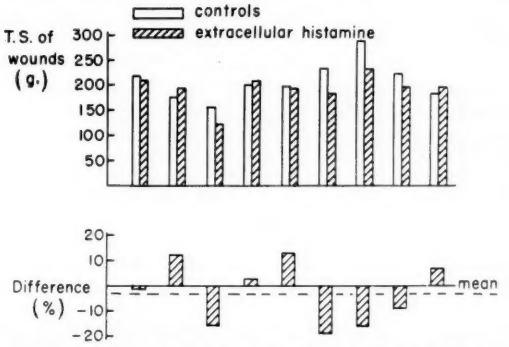

Fig. 7—Healing under the influence of extracellular histamine.

Discussion

The nature of the relation between H.F.C. and reparative growth will remain vague until essentials of the biochemical machinery involved in wound repair have been elucidated. As a working hypothesis one may assume that the effective H.F.C. is located within the cells at sites specifically concerned with initiating and sustaining rapid tissue growth. The histamine which is constantly formed and concentrated, and which promotes growth at these specific sites, is continuously disposed of by diffusion, catabolic enzymes, urinary excretion, and other devices. This speculation, supported by the experi-

ments with extracellular long-acting histamine, implies that only intracellular histamine, formed at and confined to the specific sites, actively promotes repair. But one must realise that rich sources of mammalian histidine decarboxylase (rat fœtal tissues, gastric mucosa, and wound tissues) have only recently been discovered; hence the substrate specificity of the enzyme remains to be defined. On this account one cannot exclude the possibility that the activated enzyme, in addition to histamine, catalyzes the formation of some other substance which promotes rapid tissue growth.

It has been variously reported that wound healing and formation of granulations is delayed under the influence of cortisone (see Dempster 1957). Furthermore cortisone has been shown to inhibit the rate of histamine formation in the skin (Schayer et al. 1955). In the light of the discovery of a close connection between rate of repair and rate of histamine formation it seems that the detrimental effect of cortisone on wound healing is at least in part due to its depressing effect on the H.F.C.

The artificially induced elevation in H.F.C. is small in comparison with the spontaneously generated enzyme activity in healing tissues. Even a moderately increased H.F.C., available at the very onset, may be helpful in triggering the mechanisms which are instrumental in rapid repair. Our colleague Dr. N. Sandberg has found by measuring the amounts that collagen and granulation tissue proper (from ivalon sponges) are formed considerably faster than normal in wounded rat skin after the H.F.C. has been raised by intraperitoneal injections of 48/80 (to be published).

Clinical Implications

Our observations have clinical significance in that it now appears possible to promote the rate of wound healing by aiding the processes seemingly connected with some essential step in rapid tissue growth. Studies of the effect of polymyxin B locally applied to a wound would be of interest. Our colleague Dr. G. L. Gisselsson, in a preliminary study, has seen encouraging results from applying polymyxin B in patients who had undergone radical mastoidectomy with subsequent free skin grafting. A more ambitious and far-reaching approach would require the preparation of a non-toxic agent which on injection would induce a general rise of H.F.C. similar to that in the " overshooting phase ". In principle then, it would be possible to promote repair and healing in every tissue and organ in which the H.F.C. could be artificially increased.

Summary

Evidence is presented that reparatively growing tissues in skin wounds in the rat produce histamine at a high rate as a result of increased histidine decarboxylase activity. The rate of healing can be augmented by artificial increase or retarded by lowering the histamine-forming capacity.

By inference the histamine-forming capacity constitutes an essential part of the biochemical machinery which initiates and sustains rapid tissue growth in healing wounds.

REFERENCES

Boyd, J. F., Smith, A. N. (1959) *J. Path. Bact.* **78**, 379.
Dempster, W. J. (1957) An Introduction to Experimental Surgical Studies. Oxford.
Gustafsson, B., Kahlson, G., Rosengren, E. (1957) *Acta physiol. scand.* **41**, 217.
Kahlson, G. (1960) *Lancet*, i, 67.
— Rosengren, E. (1959) *Nature, Lond.* **184**, 1238.
— — Westling, H. (1958) *J. Physiol.* **143**, 91.

References continued at foot of next column

ACUTE ADRENAL INSUFFICIENCY AFTER STEROID THERAPY

IN THREE ASTHMATICS WITH PNEUMONIA

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PATIENTS who have had steroid therapy are liable to acute adrenal insufficiency if exposed to stress. In most episodes the precipitating factor is a surgical operation (*Lancet* 1957). Chronic asthma is often associated with pulmonary or bronchial infection; and, since steroids are known to encourage the spread (often symptomless) of infection (*British Medical Journal* 1954), frequent reports of hypoadrenal collapse from the stress of pneumonia in asthmatics treated with steroids might be expected. But this is not so; hence the following three cases are of interest.

THE FIRST CASE

A girl, aged 16, had been an asthmatic since she was 2 years old. Her spasms were not controlled by the usual remedies, nor by a spell in a special residential school. In October, 1956, when she was 14, cortisone was given in a dosage of 50 mg. daily. Several attempts to reduce the dose were unsuccessful. An attack of status asthmaticus in January, 1958, necessitated admission to hospital. In April, after 18 months on cortisone, a course of corticotrophin was begun, but not until after some thirty-five injections of 40 units of ' Acthar Gel ', extending over 15 weeks, was cortisone finally stopped. This was because of the tendency for bronchial spasm to recur when cortisone was reduced, despite corticotrophin cover. The last dose of corticotrophin was given early in August.

On Oct. 2 the patient went to school as usual, although her mother had noticed that she had been slightly wheezy during the past few days. At about 11 A.M. she began to feel " very cold ", and was sent to lie down in the sanatorium. Later in the morning her father took her home. By afternoon she had become worse, being " more collapsed ". At 4 P.M. she vomited, and by 5.20 P.M. she no longer recognised her mother. At 7.30 P.M. she passed a loose foul-smelling motion, and at 11 P.M. she was taken to hospital.

The patient was unconscious. Her skin was cold and clammy, and her breathing was noisy and grunting, with shallow respiratory excursions. The alæ nasæ were working and her lips and cheeks were cyanosed. Systolic blood-pressure was about 40 mm. Hg, and the pulse-rate was 110 per min. The axillary temperature was 100°F. The left lung base was slightly dull, with reduced air entry. The abdomen was scaphoid but otherwise normal. The pupils were symmetrical, but they reacted sluggishly. Tendon reflexes were present but hard to elicit. The findings at lumbar puncture were normal, and the white-cell count was 17,000 per c.mm., with 75% polymorphs.

The girl was placed in an oxygen tent, the bottom of her bed was blocked, and treatment was begun for acute adrenal insufficiency caused by intercurrent infection, as shown in the figure. After about 4 hours she improved enough to respond to commands. 6 hours later she was conscious and able to complain

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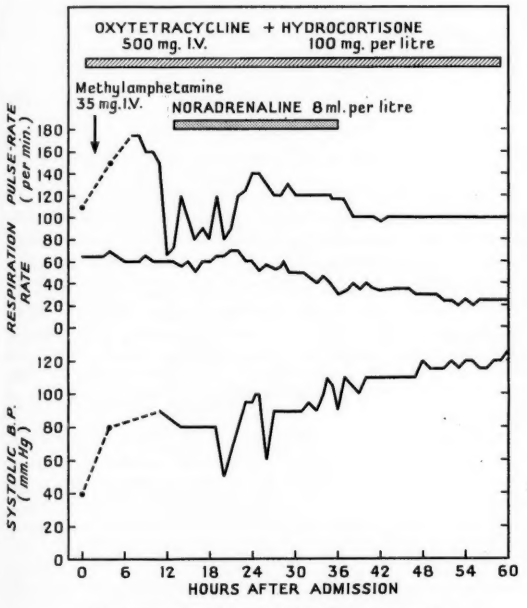
PROF. KAHLSON AND OTHERS : REFERENCES—*continued*

— — — White, T. (1958) *ibid.* **144**, 337.
— — White, T. (1960) *ibid.* **151**, 131.
Lindell, S. E., Rorsman, H., Westling, H. (1959) *Experientia*, **15**, 31.
Sandblom, P., Petersen, P., Muren, A. (1953) *Acta chir. scand.* **105**, 252.
Schayer, R. W. (1956) *Amer. J. Physiol.* **187**, 63.
— Ganley, O. H. (1959) *ibid.* **197**, 721.
— Rothschild, Z., Bizony, P. (1959) *ibid.* **196**, 295.
— Smiley, R. L., Davis, K. J. (1955) *Proc. Soc. exp. Biol., N.Y.* **87**, 590.
— Wu, K. Y. T., Smiley, R. L. (1954) *Amer. J. Physiol.* **179**, 481.
White, T. (1959) *J. Physiol.* **149**, 34.



The treatment given, and its effects in case 1.
The interrupted lines indicate that readings were unobtainable.

of generalised muscular aches. She was still cyanosed. A chest radiograph (portable) showed consolidation in the left middle and lower zones. Her condition continued to improve gradually. 2 days after admission she had begun to take fluids by mouth, and on the 3rd day the drip was discontinued. She was then given oxytetracycline by mouth 250 mg. 6-hourly, and steroids, as follows:

Hydrocortisone intramuscularly 100 mg. 8-hourly for 24 hours; then 50 mg. 6-hourly for a further 24 hours;

Prednisolone by mouth 20 mg. 8-hourly for 24 hours, and then 10 mg. 6-hourly.

A chest radiograph on Oct. 6 showed that the pneumonia was resolving, and on Oct. 8 the dose of prednisolone was reduced to 5 mg. 6-hourly.

No pathogens were found at any time in the sputum. Apart from some left-sided pleural pain on Oct. 12 the patient made an uninterrupted recovery and she was discharged home on Oct. 21 on triamcinolone 2 mg. b.d. and corticotrophin 40 units weekly. She was readmitted to hospital for further assessment when her general condition was fairly good and resolution of her chest lesion was almost complete. The eosinophil-count was 1450 per c.mm. before 20 units of corticotrophin intravenously, and 1100 per c.mm. afterwards. In February, 1959, she was again admitted for 10 days with bronchitis and asthma following influenza, and for 3 days in June with an acute attack of asthma. In August, when the patient's condition was reassessed it had improved. Her chest radiograph was now clear. She was last seen in September, when she was well and free from spasm, taking methylprednisolone 4 mg. b.d. and acthar gel 20 units fortnightly.

THE SECOND CASE

A woman, aged 37, had had asthma since the age of 5 years. For about 7 years she had used steroids to break severe attacks of spasm. An intelligent woman, she controlled her own cortisone dosage, taking 10-day courses beginning with a daily dose of 300 mg., and reducing it by about 25 mg. each day; this she had found to be the smallest effective dosage. Such courses might be required as often as twice a month, or as seldom as once in 3 months. She had had right middle and lower lobe pneumonia in 1956, and had been admitted with status asthmaticus in 1948 and 1955.

The patient was admitted to hospital on April 23, 1959. She had taken no cortisone for some 5 weeks, during which she had felt particularly well. At 10.30 A.M. the previous day, she began to have central abdominal pain with nausea. She vomited repeatedly throughout that day and night. On the morning of admission she had left-sided pleuritic pain. During the day she sweated and became increasingly breathless.

She was pale and looked shocked; she was dyspnœic but not cyanosed. Her temperature was 98°F (she was apyrexial throughout). Chest expansion was reduced on the left, with impaired percussion note and bronchial breathing over the left lower posterior chest. Musical expiratory rhonchi were heard all over the lungs. The breath smelt of acetone, the abdomen was lax, and bowel sounds were present. The other systems were normal.

On admission the total leucocyte-count was 24,700 per c.mm. The serum-electrolyte values (mEq. per litre) were: chlorides 96, potassium 3·4, and sodium 127. Chest radiography showed consolidation in the dorsal segment of the left lower lobe. Immediately on admission an intravenous drip was begun and treatment was given as for the previous case, except that erythromycin was given instead of oxytetracycline. The patient improved steadily from the first few hours after admission. Next day her total white-cell count was 15,000 per c.mm., with 84% polymorphs. Her serum-electrolytes were normal. 6 days after admission resolution of her chest was complete radiographically. The sputum never grew pathogens. Erythromycin was continued for a total of 6 days, while the dose of prednisone was reduced progressively from 60 mg. to 20 mg. daily at the time of discharge. The patient is now free of spasm, and is still taking prednisolone 10 mg. daily.

THE THIRD CASE

A man of 55 had had asthma for about 4 years. Between February and September, 1959, he was admitted to hospital in status asthmaticus three times. The first time steroids were not used; the second time prednisone was given but was not continued after discharge; and the third time prednisone was again used and was continued as a maintenance dose of 15 mg. daily, after his discharge on Sept. 18.

The fourth admission to hospital was on Nov. 25. The patient had been off work for 2 weeks with a mild exacerbation of asthma. He awoke at 4 A.M. on the morning of admission, with a rigor, right-sided pleurisy, and dyspnœa. He vomited repeatedly. His temperature at home was 100·6°F.

When admitted to hospital the patient was cyanosed, with a greyish tinge, and his temperature was subnormal. He was dyspnœic, with rales and rhonchi all over the lung fields. There was dullness at the right base posteriorly. The pulse-rate was 120 per min., and the systolic blood-pressure was 55 mm. Hg on admission. No further blood-pressure readings could be obtained. The patient was given hydrocortisone 150 mg. intravenously, and 100 mg. intramuscularly. An intravenous drip was set up, containing metaraminol bitartrate 50 mg. in 500 ml. dextrose saline. Intramuscular tetracycline was also given, and oxygen was administered via a tent. The patient did not respond to any of these measures, nor to a direct intravenous dose of 5 mg. metaraminol. 2 hours later he died.

At postmortem the only abnormal signs were in the respiratory system. Diffuse tracheobronchitis and bilateral basal bronchopneumonia were found, with bronchiectatic changes in the lower lobes and right upper lobe. The remaining lobes were œdematous. Small emphysematous cysts were seen over the surface of the left lung. The pleuræ were normal. The adrenals were of normal size, with thin cortices but normal pigmentation; sectioning revealed no significant abnormality.

Discussion

Several patients with rheumatoid arthritis who were having long-term cortisone treatment have died of pneumonia which was accompanied initially by only slight symptoms. Three such cases are described by Jacobs and Rose (1955), four by Page (1954), and another by Bunim (1951).

Savidge and Brockbank (1954) describe two deaths in asthmatics treated by steroids, and give brief details of eight further examples from previous reports. In seven of these ten cases postmortem examinations were made, but significant infection was not found, the most common pathological process being widespread plugging of the bronchi by mucus. One asthmatic having steroids died from pulmonary embolus (Allanby 1957). During the Medical Research Council trials of cortisone in asthma (1956) a chronic asthmatic died of status asthmaticus, and another died during the treatment of status asthmaticus; " a large infective element " was noted in the latter. Pearson (1959) mentions a patient with severe recurrent asthma who died while taking corticotrophin. Postmortem revealed an unsuspected and symptomless right-upper-lobe pneumonia.

The pneumonia in the three patients described above was not symptomless, although it was overshadowed clinically by the adrenal collapse. Two of the three patients were not taking steroids when they became ill; in case 1 they had been withdrawn 8 weeks before the onset of symptoms, and in case 2 five weeks before. However, the third patient died 13 weeks after beginning a continuous course of prednisone, and he had more definite signs of acute chest infection than did the other two. This patient's adrenals were within normal limits anatomically. The adrenals of the cases referred to above were either normal or atrophic. In one case (Jacobs and Rose 1955) " atrophy with hæmorrhage " was found.

To prevent such incidents steroid therapy for young asthmatics, in whom there is ample opportunity for the adrenals to atrophy, should clearly be avoided when possible. On the other hand asthma had incapacitated all these patients, and cortisone was used in an attempt to produce a relatively normal life only after other measures had failed. The second patient regards her recent illness as a small price to pay for a means of breaking resistant spasm. Her dosage of steroids and frequency of courses correspond approximately with those said not to affect the adrenal cortex adversely (*British Medical Journal* 1958). The first patient had a long course of corticotrophin after her 18 months' treatment with cortisone. Her experience supports that of the workers cited by Bayliss (1958), who regard exogenous corticotrophin as doing no more than depressing the pituitary/adrenal system at a different point. Closer supervision would be of little help in preventing such a catastrophe, because the onset is so sudden. But recognition of the need for prompt treatment in a patient collapsed and vomiting, and who has had steroid therapy, is all-important. An ampoule of hydrocortisone hemisuccinate is well worth inclusion in the emergency bag, since, whatever serious illness may overwhelm the patient treated by long-term steroid therapy, adequate assistance of adrenal function will certainly be required.

Summary

Acute adrenal insufficiency associated with pneumonia developed in three asthmatics who had had steroid therapy. Symptoms and signs of infection were overshadowed by those of hypoadrenal collapse. Two patients recovered after supportive therapy. Early recognition and treatment of such cases is important.

I should like to thank Dr. John Lister for his encouragement and interest; Dr. George Hadley, Dr. G. T. Thomas, Dr. P. H. Willcox, and Dr. Brian Thompson for allowing me to describe their cases; and Mr. Peter Fiske of the photographic department for his help with the charts.

References at foot of next column

DURABILITY OF SUTURE MATERIALS

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THE surgeon often requires a suture which will maintain its strength when buried in the tissues. Many new materials are now available; and, in order to assess the ability of these to retain their tensile strength, we have inserted eight types of suture in the abdominal wall of the dog, testing them after periods of up to twelve months. Furthermore, the effect of knot-tying on the tensile strength of the suture has been studied.

Methods

Tensile Strength

In the first part of the investigation, all the threads studied were sterilised by boiling and placed with aseptic precautions and without tension in the subcutaneous tissues or rectus sheath; in some cases the fibres were wound on bobbins before insertion. After varying periods they were removed, adherent fibrous tissue was removed as far as possible, and their tensile strength at breaking-point was measured with a Hounsfield tensometer (fig. 1). Representative samples boiled for as long as were the implanted specimens were also tested to ascertain the materials' original strength.

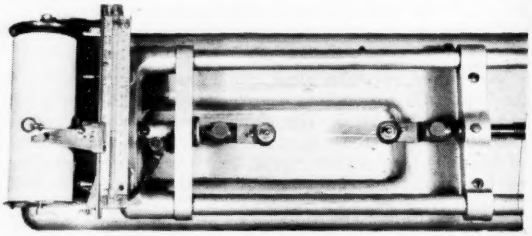

Fig. 1—A fibre in the Hounsfield tensometer, the tightening gear being out of the picture on the right.

The following fibres were studied:

Nylon.—Two sizes of monofilament nylon were used: (*a*) purple, size 3N, 0·009 in. diameter; (*b*) blue, size 2N, 0·007 in. diameter. The dyes used to colour the nylon are classified as Vat dyes, but we were unable to ascertain their nature. Such monofilaments were inserted into 15 animals and removed two to twelve months later.

Polyethylene.—A high-density, high-melting-point polyethylene monofilament (' Courlene X3 '), of 0·010 in. diameter, was placed in 14 animals and examined four to twelve months subsequently. This material contains no dicetyl phosphate, which is known to be a fibrogenic agent.

Polypropylene.—This new monofilament fibre of 0·010 in. diameter became available towards the end of this study and was inserted into only 2 animals and was left in situ four months.

' *Teflon* ' (polytetrafluoroethylene).—Two types of unbleached multifilament tetrafluoroethylene thread of 400 denier, each containing 60 filaments, were studied: (*a*) " Undoubled " (i.e., having only one twist per in.); (*b*) " Doubled " (having 4·2 twists per in.). Neither of these had any finishes applied to them in manufacture. 13 animals received the undoubled and 10 animals the doubled material; both groups were studied up to twelve months subsequently.

DR. STEVENS: REFERENCES

Allanby, K. D. (1957) *Lancet*, i, 1104.
Bayliss, R. I. S. (1958) *Brit. med. J.* i, 935.
British Medical Journal (1954) i, 381.
— (1958) i, 1166.
Bunim, J. J. (1951) *Proc. clin. ACTH Conf.* **1**, 482.
Jacobs, J. H., Rose, F. C. (1955) *Tubercle, Lond.* **36**, 113.
Lancet (1957) ii, 130.
Medical Research Council (1956) *Lancet*, ii, 798, 803.
Page, J. A. (1954) *Brit. med. J.* ii, 1334.
Pearson, R. S. B. (1959) *Post Grad. med. J.* **35**, 463.
Savidge, R. S., Brockbank, W. (1954) *Lancet*, ii, 893.

PROPERTIES OF SYNTHETIC FIBRES STUDIED

Fibre	Melting point (°C)	Specific gravity	Water absorption (%)	Acid resistance	Alkali resistance	Strength (g. per denier)	Extension at break (%)
Nylon	250	1·14	4	Poor	Good	4·3–8·8	22
Polyethylene	(softens at 120)						
'Courlene X3'	135	0·96	0	Excellent	Excellent	4–6	20–25
Polypropylene	165	0·90	0	Excellent	Excellent	3·5–6	..
Teflon	400	2·2	0	Excellent	Excellent	1·5	13
Terylene	249	1·38	0·4	Good	Good	4·5–7·5	40
Orlon	230	1·17	1·2	Very good	Fairly good	5	18

'*Terylene*'.—Three-cord multifilament white terylene was used. During manufacture the thread is first scoured with detergent 'Lissapol N.C.' and a little ammonia to remove any lubricant or antistatic agent present. The white appearance is obtained by use of a fluorescent dye—'Uvitex E.R.' (of 'Ciba Clayton'). In the spooling operation the thread is run over paraffin-wax discs, which contain 2% of silicone fluid, the amount of wax taken up being about 1% of the thread's finished weight. The resulting material was inserted into 17 animals and removed two to twelve months later.

'*Orlon*'.—Three-cord 100-denier multifilament orlon thread was inserted into 10 animals and studied up to nine months later. In its final manufacturing process this thread has been scoured by boiling water and soap to remove all finishes.

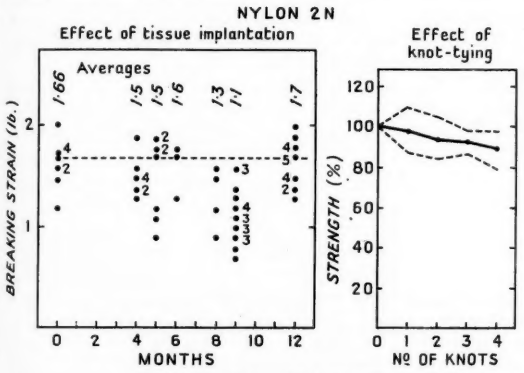

Fig. 2—Findings with nylon 2N.

On the left hand graph each point represents the breaking strength of a segment of thread, removed from the tissues after the period indicated. The points at zero months represent the strengths of specimens of the unused material. The small figures against some points show the number of segments having that breaking strength.

The effect of knot-tying (see text) is shown on the right. The continuous line represents the average strength of six specimens taken from three lengths of suture after each knot had been tied, the average initial strength being taken as 100%. The interrupted lines are the maxima and minima of the six lengths tested on each occasion.

Linen thread.—During manufacture this material is first boiled in a sodium-hydroxide solution to remove impurities from the natural flax, and then washed with acid and water. It is then dyed with an anthraquinone dyestuff, the thread taking up about 2% of its weight of this. Finally a "suture finish" is applied based on carboxymethyl cellulose; about 1% of this finish, calculated on the weight of the thread, is applied in this process. This linen suture thread was placed in 14 animals and studied up to twelve months later.

Silk.—Black braided silk (size 4/0), treated only with a logwood dichromate dye, was put into 11 animals and tested up to twelve months subsequently.

Effect of Knot-tying

In the second part of the investigation new fibres only were studied. It was hoped to reveal the effects of the trauma inflicted on a suture by repeated knot-tying, since after a knot has been tied the remainder of the thread is often reused. Three representative lengths of suture were taken, and one piece was cut from each for a single initial tensile-strength measurement. The remainder had two simple knots, to make a reef-knot, run down with a finger the entire length of the ends. Segments were cut off each end, and their breaking strength was measured. This process was repeated until four separate reef-knots had been tied and four sets of readings obtained. The test was carried out with the threads dry. No attempt was made to tie these knots in a "non-traumatic" way—they were tied as might be done at operation. Resulting knot-strength was not tested. The following sutures were involved in this part of the experiment: nylon, polyethylene, polypropylene, teflon, terylene, orlon, linen thread, and silk.

Results

Nylon.—The breaking-strain figures for the two sizes of nylon studied are shown in figs. 2 and 3, in each case the control values being given at "0" months. While the smaller size (blue 2N) did not lose its colour after insertion in the tissues, the larger size (purple 3N) became patchily discoloured, and where this had occurred the fibre broke on testing. The behaviour of the two types is somewhat different: the thicker fibre seems to have gained in strength during its period in the tissues; whilst the thinner fibre has lost strength, particularly in the specimens studied after eight and nine months. In both cases, the variations in strength are greater after tissue implantation than in the unused material, which itself shows quite a variation in different pieces.

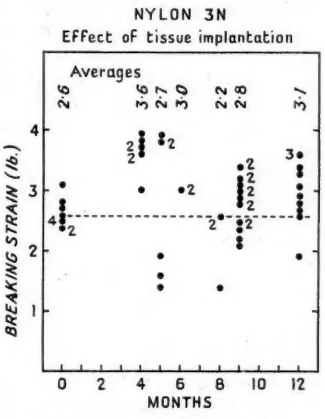

Fig. 3—Findings with nylon 3N.

A length of heavy (green) nylon suture not included in this study was recovered undiscoloured from the abdominal wall of a patient twenty-eight weeks after its insertion. It broke

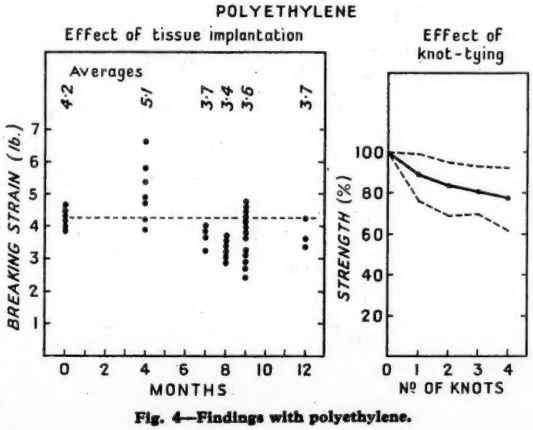

Fig. 4—Findings with polyethylene.

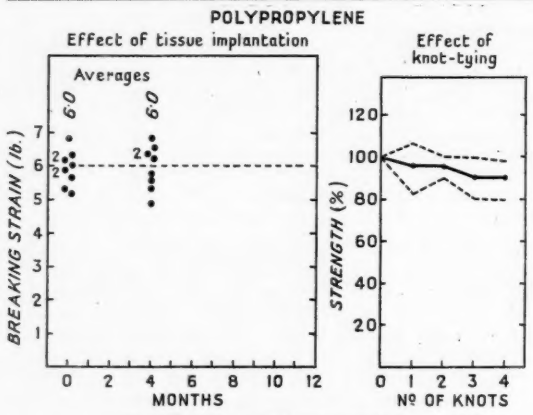

Fig. 5—Findings with polypropylene.

under a load of 16·4 lb. Five lengths of unused similar material broke at 17·5, 16·7, 17·2, 17·5, and 16·9 lb.

The effect of knot-tying on nylon was studied on the blue (2N) variety only. This monofilament did not show any signs of fraying on its surface as a result of the knot-tying, but did become curly and lost an average of 12% of its tensile strength after four knots had been tied.

Polyethylene.—The behaviour of the polyethylene studied is shown in fig. 4, which shows that there is considerable variation in the strength of different segments of this monofilament. The effect of tying of four separate knots on this type of fibre is also shown in fig. 5. This monofilament became obviously somewhat

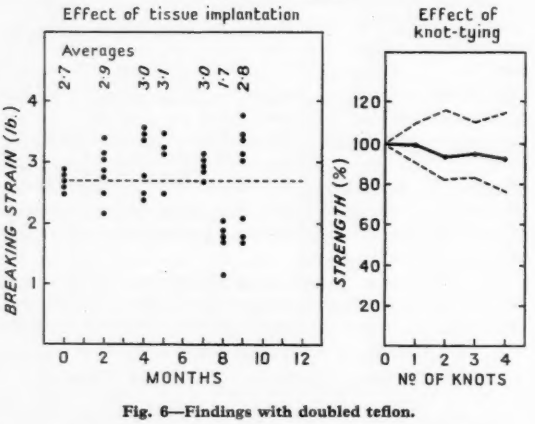

Fig. 6—Findings with doubled teflon.

"furry" during the tying of the first knot, and further knotting not only made this more noticeable but was associated with reduced tensile strength; after four knots, an average of 21% of the initial breaking-strength had been lost—the poorest behaviour of the three monofilaments investigated.

Polypropylene.—This, the third, monofilament was studied after only four months in the tissues (fig. 5) and did not lose any of its initial strength in this time. Knot-tying affected this material least of all the monofilaments both as regards strength and surface condition, which did not alter obviously during this trauma.

Teflon.—This proved the most difficult material to study as it shredded with the utmost ease even when "doubled", being akin to "floss silk" in its texture. This characteristic made dissection of the implanted sutures infiltrated with connective tissue virtually impossible as regards the undoubled teflon, and only when the doubled material had been wound on to bobbins before implantation was subsequent dissection feasible. Specimens left in the tissues for only up to nine months therefore were available for study. Fig. 6 shows that teflon has been little affected by the tissues. The increased strength of some specimens over the unused controls is probably due to contained fibrous tissue and weakening of others to shredding of the material during dissection. Although knot-tying also tended to shred this multifilament despite its slippery properties, it lost only 9% of its original strength after four knots.

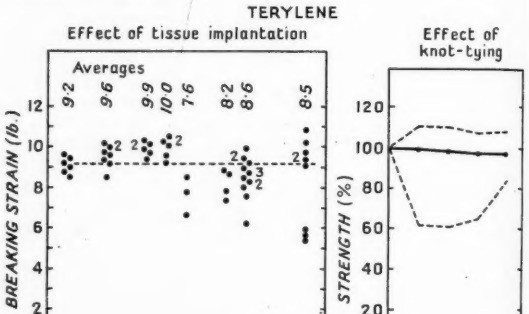

Fig. 7—Findings with terylene.

Terylene.—The results (fig. 7) indicate that very probably there has been a very slight tissue effect within twelve months. Although the range of strengths of the "control" material is small, our studies with knot-tying indicated that this thread might weaken quite considerably with slight trauma along a short length; this is shown by the minimal strength percentages of the "knot-tying" graph. Here, although knot-tying seems to have caused little weakening as judged by the average figures, surprisingly low strengths were noted, which may simply reflect the inconstancy of the thread studied.

Orlon.—The behaviour of orlon during nine months in the tissues (fig. 8) suggests some initial weakening after the short period of two months without further degeneration. Knot-tying undoubtedly weakens the thread—

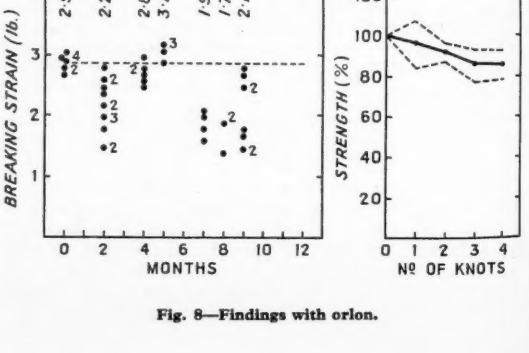

Fig. 8—Findings with orlon.

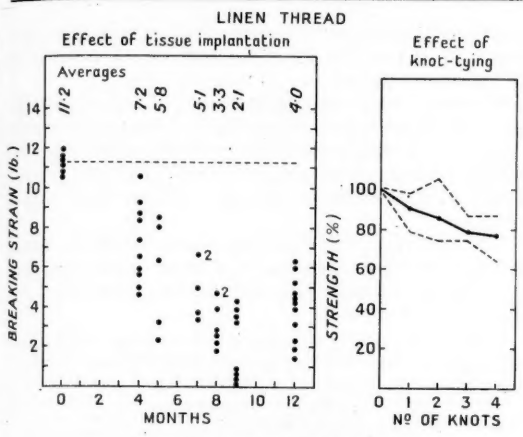

Fig. 9—Findings with linen thread.

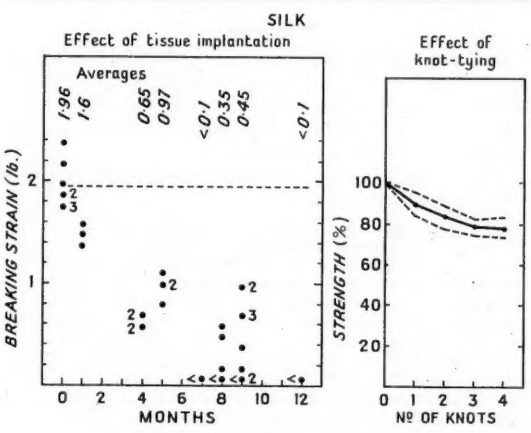

Fig. 10—Findings with silk.

13% after four—but the maximum and minimum figures suggest that the tested material was considerably more homogeneous than the terylene studied.

Linen thread.—It is evident that this natural fibre degenerates rapidly in the tissues (fig. 9), some segments having less than 5% of their original strength within nine months of tissue implantation. Four knots tied with this thread caused an average loss of 23% of its original strength, one piece losing 36% after this trauma.

Silk.—With 4/0 silk there was complete loss of strength in as short a time as seven months (fig. 10), and all material remaining longer contained completely degenerate sections. Here again, the tying of knots with the suture led to considerable weakening—22% after four. It was, however, much more homogeneous than linen thread as regards its response to the tying of knots.

Discussion

When sutures are to be buried in the tissues by the surgeon, their possible irritative effects must be considered, together with their ability to retain sufficient strength for an adequate period. This last aspect has alone been studied here.

It is obvious from this study that the man-made fibres are superior to either linen or silk if a period of persistence over six months is required. Of the synthetic fibres, nylon is still predominantly used by the surgeon. It has been known for several years that multifilament nylon loses up to 80% of its strength within twelve months (Harrison and Adler 1956, Catchpole and Curran 1958); this precludes its use if indefinite maintenance of strength is required. In contrast, monofilament nylon loses very much less strength, probably because of the smaller surface area exposed to the corrosive effects of tissue-fluids (Edwards and Lyons 1958). Possibly the colouring and other agents used in the production of these nylon filaments may modify their resistance to the tissue environment—a view which receives some support from the observation that the purple dyed nylon used here exhibited discoloured patches along its length and proved weakest at these sites.

Of the three monofilaments studied, polypropylene holds great promise as a suture material. Chemically it is extremely stable, is readily autoclaved, and, although studied after only four months in the tissues, it then behaved as the unimplanted material. It resists the trauma of knot-tying extremely well and probably produces little if any tissue reaction, although this remains to be studied. Furthermore, it is cheaper to manufacture than nylon. High-melting-point polyethylene seems in general to be inferior to polypropylene as a suture.

If a " floss " type of suture is required, the undoubted durability of undoubled multifilament teflon can be guaranteed to outlast silk, which degenerates extremely rapidly. But the cheaper, multifilament, high-melting-point polyethylene can be currently obtained; and multifilament polypropylene, when available, may supplant even this.

There seems to be little to choose between the " corded " synthetic multifilaments, terylene and orlon, although the average performance of terylene in the tissues is perhaps slightly superior to that of orlon. The range of strengths after any given period of implantation is wide in both cases. This is perhaps understandable regarding the terylene studied here, for it was not of surgical quality, whilst the orlon had been specially prepared. Chemically, terylene might be expected to hydrolyse in the mildly alkaline tissue environment (Harrison et al. 1957).

The rapid weakening of linen thread has both advantages and disadvantages. It can be relied on to break up rapidly in an alimentary-tract suture line, but will certainly persist sufficiently long for the slowest healing abdominal wound to become sound.

The use of silk to suture arterial grafts to the host vessel is perhaps curious. It is now well known that the material for synthetic arterial prostheses must be chosen with great care. Little attention, however, has been drawn to the advisability of using a fibre other than silk for stitching them in place, even though Douglas showed in 1949 that silk, as well as linen thread, rapidly weakens in the tissues—findings confirmed in the present study. It should further be borne in mind that the tying of knots with this material rapidly weakens it, and it is desirable not to use the same suture for more than two or three interrupted stitches, unless the traumatised length is avoided in the actual stitch.

In conclusion, the behaviour of fibres in the tissues is closely related to their intrinsic properties and these generally depend on their chemical constitution. How they stand up to the trauma involved in the tying of knots does not seem to depend directly on whether they are used as monofilaments or multifilaments, whether " undoubled " or prepared as corded thread.

Summary

Six man-made and two naturally occurring fibres were inserted into animal tissues for periods of up to twelve months, their tensile strengths being measured before and after implantation. The effect of knot-tying on tensile strength was also studied.

The naturally occurring fibres compared unfavourably with the synthetic ones.

We are very grateful to Prof. R. P. Jepson and Prof. A. W. Kay for every encouragement during this investigation; to Prof. A. G. Quarrell for permission to use the Hounsfield tensometer in his department; to the animal-house staff of the university for the care of our animals; and to the department of photography of the Royal Infirmary for help with the illustrations. The following manufacturers have given us much information concerning their products and in several cases have supplied the material investigated: A. Browne Ltd., and Imperial Chemical Industries Ltd. (nylon); Courtaulds Ltd. (polyethylene and polypropylene); Du Pont Ltd. (undoubled 'Teflon'); Fothergill and Harvey Ltd. (doubled 'Teflon'); John Dewhurst and Sons Ltd. ('Terylene'); J. and P. Coats Ltd. ('Orlon'); William Barbour and Sons Ltd. (linen thread); and Ethicon Ltd. (silk). The 'Orlon' was kindly supplied through the courtesy of Prof. J. B. Kinmonth.

REFERENCES

Catchpole, B. N., Curran, R. C. (1958) *Surgery*, **44**, 994.
Douglas, D. M. (1949) *Lancet*, ii, 497.
Edwards, W. S., Lyons, C. (1958) *Surg. Gynec. Obstet.* **107**, 62.
Harrison, J. H., Adler, R. H. (1956) *ibid.* **103**, 613.
— Swanson, D. S., Lincoln, A. F. (1957) *Arch. Surg., Chicago*, **74**, 139.

SULPHÆMOGLOBINÆMIA AND GLUTATHIONE

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WHILE determining the range of erythrocyte-glutathione concentrations in normal people and in patients with drug-induced hæmolytic anæmia, I noted a high level of reduced glutathione in the blood of a patient with sulphæmoglobinæmia. This prompted investigation of other cases of sulphæmoglobinæmia, and in some of these a similar high level of reduced glutathione was found.

Reduced glutathione (G.S.H.) is a tripeptide of cysteine, glutamic acid, and glycine, and it contains a sulphydryl group. It is present within the erythrocytes and is not normally found in the plasma. Low blood levels of G.S.H. are a feature of certain types of drug-induced hæmolytic anæmia (Beutler 1955).

Ideas on the ætiology of sulphæmoglobinæmia have changed little since 1922, when Snapper showed that dogs given phenacetin and precipitated sulphur by mouth developed sulphæmoglobinæmia within a few days, whereas those given only phenacetin or other aniline derivatives developed methæmoglobinæmia (cited by Archer and Discombe 1937). These findings were confirmed by Harrop and Waterfield (1930), who in addition found that acute hydrogen-sulphide poisoning in dogs (as a result of rectal administration of the gas) did not produce sulphæmoglobinæmia, even though the dogs were receiving aniline derivatives as well and were showing various grades of methæmoglobinæmia at the time. Harrop and Waterfield concluded that the reaction between hæmoglobin and sulphide to produce sulphæmoglobin was a slow one, and that, as hydrogen sulphide was rapidly excreted, sulphæmoglobin would not be formed unless sulphide was continuously absorbed from the bowel over a long period. 6 of their 10 patients with sulphæmoglobinæmia had chronic constipation, and this was held responsible for a constant excess production of hydrogen sulphide.

The drugs which may produce either methæmoglobinæmia or sulphæmoglobinæmia include phenacetin (usually compounded with codeine), acetanilide, sulphonal, isoniazid, nitrites, pamaquin, stibophen, and some of the earlier sulphonamide compounds (Whitby and Britton 1957).

The neat theory that constipation gives rise to hydrogen sulphide, which in the presence of certain drugs produces sulphæmoglobinæmia, is not altogether satisfactory, for the following reasons:

1. Constipation is by no means always present, and may be a side-effect of the medicine ingested rather than a cause of sulphæmoglobin formation. Constipation was present in only 26 of 62 patients with sulphæmoglobinæmia reported by Brandenburg and Smith (1951).

2. Haggard (1921) showed that, in the presence of oxygen, blood-plasma rapidly oxidises hydrogen sulphide, and that "in vivo the gas [H_2S] can exhibit no cumulative action when inhaled".

3. Harrop and Waterfield (1930) also found that they could produce sulphæmoglobinæmia in splenectomised dogs by feeding sulphur alone: when sulphur was fed to normal dogs, no change occurred in the blood.

4. Occasionally cases are recorded in which apparently no drugs have been taken. Miller (1957) reported a case of congenital sulphæmoglobinæmia in a cyanotic newborn infant where there was no history of drug-taking by the mother. The father's blood contained 1·4 g. sulphæmoglobin per 100 ml.; he appeared cyanotic, and he gave a history of several other "blue" members of the family.

5. Sulphæmoglobinæmia is relatively uncommon despite the widespread use of drugs such as phenacetin; and there is no obvious correlation between dosage or duration of use of the drug and the appearance of the abnormal pigment.

These findings suggest:

1. That some factor peculiar to the individual other than drugs and a source of hydrogen sulphide, may determine susceptibility to sulphæmoglobin formation.

2. That the bowel is unlikely to be the source of hydrogen sulphide, which is readily and rapidly eliminated from plasma.

Further evidence to support and elaborate these statements is presented in this paper.

The Investigation

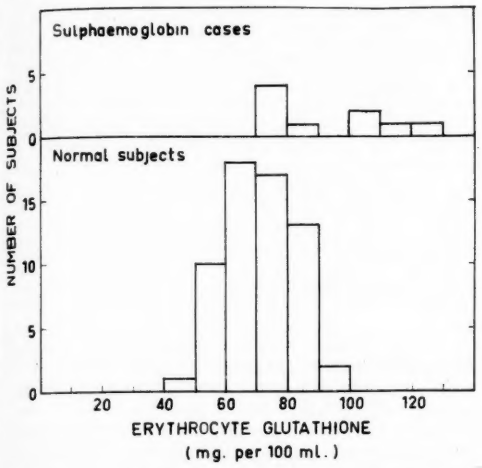
The concentration of G.S.H. in the blood was measured by Beutler's (1957a) modification of the nitroprusside method of Grunert and Phillips (1951) and expressed in mg. G.S.H. per 100 ml. packed erythrocytes.

The average blood-G.S.H. of 61 "normal" hospital patients proved to be 70 mg. per 100 ml. erythrocytes, with a standard deviation of 11·5 and a range of 42 to 93 (see figure).

9 female patients who either had sulphæmoglobinæmia at the time of examination, or who had recently been reported as having sulphæmoglobinæmia, were reviewed. Their blood-G.S.H. values (see also figure) were:

Case	G.S.H. (mg. per 100 ml. packed erythrocytes)	Case	G.S.H. (mg. per 100 ml. packed erythrocytes)
1	117	6	121
2	100	7	74
3	84	8	76
4	101	9	74
5	72		

4 of these patients (nos. 1, 2, 4, and 6) had values well above the normal range. Of the 5 who were within it, 2 had shown methæmoglobin as well as sulphæmoglobin.



Reduced-glutathione (G.S.H.) concentrations in the erythrocytes of 61 normal subjects and 9 patients who had sulphæmoglobinæmia.

Case-reports

CASE 1.—Aged 43. Presented with anæmia and cyanosis. The absorption band of sulphæmoglobin, persisting after the addition of potassium cyanide, was seen on the Hartridge spectroscope. She was an asthmatic, taking one 'Rensop' powder (containing phenazone, iodopyrine, caffeine, and antipyrine acetosalicylate) each morning for six years, and an occasional aspirin tablet. She was not constipated but regularly took 'Epsom Salt'.

CASE 2.—Aged 46. Had cyanosis and sulphæmoglobin three years ago, after ingestion of a large number of 'Veganin' tablets (containing acetylsalicylic acid, phenacetin, and codeine phosphate) for "rheumatism". No sulphæmoglobin was detectable when the blood-G.S.H. was done, though she was still consuming a large number of aspirin, phenacetin-caffeine tablets each day for headaches. She was not constipated.

CASE 3.—Aged 79. Osteoarthritis. Had been taking tab. codein. co. *B.P.* for years. Cyanosis and sulphæmoglobin were detected. She said that she was never constipated and did not take medicine for the bowels.

CASE 4.—Aged 88. Was taking tab. codein. co. for headaches. Cyanosis and sulphæmoglobinæmia. No methæmoglobinæmia.

CASE 5.—Aged 76. Cervical spondylosis. Had been taking tab. codein. co. two tablets six-hourly for two and a half weeks before central cyanosis was noted. Spectroscopy showed both methæmoglobin and suphæmoglobin.

CASE 6.—Aged 51. Rheumatoid arthritis, was taking tab. codeine co. for pain. Sulphæmoglobin had been detected three months previously, was not present at the time blood-G.S.H. was determined. She was constipated and took laxatives.

CASE 7.—Aged 76. Admitted with bilateral infected varicose ulcers. She had been taking tab. codein. co. for pain (six daily). Her blood contained 5% methæmoglobin and 6% sulphæmoglobin at that time—seven months before the blood-G.S.H. was estimated. She was not constipated, but took Epsom salt or 'Alophen' every third night.

CASE 8.—Aged 65. Had been taking six to eight 'Angesil' tablets each day (containing acetylsalicylic acid, phenacetin, and codeine phosphate) for pain in the throat. She was not constipated but took Epsom salt every day. A cyanotic tinge was noted and sulphæmoglobin was reported two months before the blood-G.S.H. estimation.

CASE 9.—Aged 65. Was taking tab. codein. co. for pain under the left shoulder. Five months later cyanosis was noted and sulphæmoglobin detected—but no abnormal pigment was present when the blood-G.S.H. was done. She had always been constipated and regularly took 'Agarol' or Epsom salt.

Discussion

The increased blood-G.S.H. level found in 4 out of 9 cases of sulphæmoglobinæmia might be regarded as

1. A chance finding.
2. Merely a secondary effect, and due possibly to anoxia.
3. A primary ætiological factor.

A Chance Finding?

Beutler (1957a) found the average blood-G.S.H. level in 153 normal people (121 Negro and 32 Caucasian) to be 67·3 mg. per 100 ml. erythrocytes, with a standard deviation of 14·7 and a range of 43–151 mg. That is to say, there were several normal people with a blood-G.S.H. level above 100 mg. per 100 ml. erythrocytes.

A similar range might have been revealed in my series had a larger number of normal controls been included. Nevertheless it seems more than fortuitous that the 4 patients with sulphæmoglobinæmia should be the only 4 to have a blood-G.S.H. level above 100 mg. The number of cases is too small for proper statistical analysis.

A Secondary Effect?

Delrue and Vischer (1933) reported an increase in the level of blood-G.S.H. in men staying at high altitude, which was not explained solely by the change in number of red cells; and according to Barron (1951) low oxygen tensions increase the G.S.H. content of many tissues. However, 2 of the present cases (nos. 2 and 6) had blood-G.S.H. values of 100 and 121 mg. per 100 ml. erythrocytes at a time when neither was anæmic, nor was sulphæmoglobin detectable spectroscopically.

A Primary Factor?

The third possibility is that G.S.H. in excess of normal may be an ætiological factor in sulphæmoglobinæmia. Attempts to establish this by in-vitro experiments tend to be unsatisfactory because:

A. The metabolic activity of blood hæmolysates differs from that of intact erythrocytes, and rapid disappearance of G.S.H. from lysed red cells cannot be prevented by the addition of glucose (Szeinberg et al. 1958).

B. Reduced G.S.H. resides within the erythrocytes, and there is no measurable G.S.H. in human plasma—nor is there any evidence that the erythrocyte membrane is permeable to G.S.H. added to the surrounding medium.

Hence the experimental addition of G.S.H. to either whole or lysed blood does not reproduce the conditions found in some of these patients.

One of the functions of erythrocyte-G.S.H. is the maintenance of sulphydryl groups. It has been suggested that G.S.H. is one of the main factors protecting hæmoglobin against oxidation by molecular oxygen (Eggleton and Fegler 1952). Fegler (1952) has shown that spontaneous oxidation of hæmoglobin to methæmoglobin is inhibited by G.S.H., and red cells in which all the hæmoglobin has been converted to methæmoglobin by sodium nitrite contain no reduced G.S.H.—the latter being converted to oxidised glutathione. It is interesting that 2 of the 5 sulphæmoglobin cases with normal G.S.H. levels also had some methæmoglobin.

What ultimately happens to oxidised glutathione (G.S.S.G.)? Some is converted back to G.S.H. via the action of the enzyme glutathione reductase (G reductase) and reduced triphosphopyridine nucleotide (T.P.N.H.). Some is presumably broken down within the cell. In the presence of a high intracellular concentration of G.S.H., it is possible that the equilibrium of the reaction:

$$\text{G.S.S.G} + \text{T.P.N.H.} + \text{H}^+ \underset{}{\overset{\text{G. reductase}}{\rightleftharpoons}} 2\ \text{G.S.H} + \text{T.P.N.}$$

is shifted to the left, and the excess G.S.S.G. is destroyed.

Flanagan, in a personal communication to Beutler (1957b), reported that cotton impregnated with silver nitrate turns black when suspended over a sample during the glutathione stability test—suggesting that G.S.S.G. may liberate hydrogen sulphide in its breakdown. If in fact it does this, a possible connection between raised erythrocyte-G.S.H. and sulphæmoglobin may be seen. In the presence of excess G.S.H., some of the G.S.S.G. formed may be broken down and hydrogen sulphide may be liberated, followed by the irreversible formation of sulphæmoglobin. The process may be accelerated by various drugs such as phenacetin.

Even in the absence of drugs, this reaction may lead to the slow continuous liberation of small amounts of hydrogen sulphide, provided the intracellular G.S.H. level is high enough. This may be the explanation of Miller's case of congenital sulphæmoglobinæmia (Miller 1957). A high blood-G.S.H. concentration could both increase the likelihood of sulphæmoglobinæmia and decrease the likelihood of methæmoglobinæmia.

Summary

1. Nine cases of sulphæmoglobinæmia are reported in which the concentration of reduced glutathione in the blood was estimated.

2. Four out of the nine patients had a raised erythrocyte-glutathione concentration, and it is suggested that this factor may increase susceptibility to formation of sulphæmoglobin.

3. Whether or not the erythrocyte-glutathione concentration is raised, the source of hydrogen sulphide for sulphæmoglobin formation is probably within the erythrocyte, rather than the bowel.

My thanks are due to Dr. T. E. Lowe and Dr. P. Fantl for helpful criticism of this paper and to Miss M. Bick for much practical advice.

REFERENCES

Archer, H. E., Discombe, G. (1937) *Lancet*, ii, 432.
Barron, E. S. G. (1951) *Advanc. Enzymol.* **11**, 253.
Beutler, E. (1957a) *J. Lab. clin. Med.* **49**, 84.
— Dern, R. J., Flanagan, C. L., Alving, A. S. (1955) *ibid.* **45**, 286.
— Robson, M., Buttenwieser, E. (1957b) *J. clin. Invest.* **36**, 617.
Brandenburg, R. O., Smith, H. L. (1951) *Amer. Heart J.* **42**, 582.
Delrue, G., Vischer, A. (1933) *C.R. Soc. Biol., Paris*, **113**, 942.
Eggleton, P., Fegler, G. (1952) *Quart. J. exp. Physiol.* **37**, 163.
Fegler, G. (1952) *Nature, Lond.* **170**, 624.
Grunert, R. R., Phillips, P. H. (1951) *Arch. Biochem.* **30**, 217.
Haggard, H. W. (1921) *J. biol. Chem.* **49**, 519.
Harrop, G. A., Waterfield, R. L. (1930) *J. Amer. med. Ass.* **95**, 647.
Miller, A. A. (1957) *J. Pediat.* **51**, 233.
Snapper, I. (1922) *Ned. Tijdschr. Geneesk.* **66**, 2541.
Szeinberg, A., Asher, Y., Chaim Sheba (1958) *Blood*, **13**, 348.
Whitby, L. E. H., Britton, C. J. C. (1957) Disorders of the Blood; p. 693. London.

ENDOCARDITIS COMPLICATED BY AGRANULOCYTOSIS

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WE describe the following case not only for its intrinsic interest but also to show that a long major illness with a very grave complication can be successfully treated in the patient's home.

Case-report

On March 5, 1959, a woman of 57 became acutely ill with fever, malaise, and general weakness. The next day a right-sided hemiplegia developed, associated with drowsiness and partial aphasia.

The patient was given crystalline penicillin 500,000 units twice daily as a prophylactic against pneumonia. An ejection systolic murmur was heard, and a systolic click was present.

On March 7 her urine was found to contain albumin and granular casts, and a midstream specimen grew a pure growth of coagulase-positive *Staphylococcus aureus* which was fully sensitive to penicillin. By the 4th day of her illness the cardiac murmur had become louder and harsher; it was audible over the whole precordium, at its loudest in the 3rd and 4th left interspaces about 3 in. from the midline, and conducted to the axilla. On searching for evidence of emboli, several splinter hæmorrhages were found in the fingernails and toenails; in addition five large Osler's nodes were discovered in the buttocks and limbs, and two of these developed small pustular heads which later dried up. Her spleen was not palpable; the hæmoglobin was 98% (14·2 g. per 100 ml.), white blood-cells (W.B.C.) 9600 per c.mm., erythrocyte-sedimentation rate (E.S.R.) 30 mm. in the 1st hour (Wintrobe), blood-urea 48 mg. per 100 ml., and serum glutamic oxaloacetic transaminase 20 units.

Diagnosis

The fever, the changing cardiac murmur, and the evidence of emboli established the diagnosis of endocarditis. The patient had no history of congenital or rheumatic heart-disease, recent sore throat, dental extractions, or septic skin conditions. Her blood-pressure, recorded several times before this illness, was in the region of 150/90 mm. Hg, and no abnormality had ever been detected in her heart. She had had erysipelas in 1955 and 1957 without cardiac complications. Nevertheless she now had an endocarditis almost certainly acute, and possibly due to the *Staph. aureus* which was isolated from her urine. The portal of entry of the pathogen into the blood-stream was impossible to discover.

We decided to stop the penicillin for 48 hours in an attempt to obtain a positive blood-culture. As the patient had already had a major cerebral embolism this was not an easy decision to take, but we were swayed by the desire to find an organism and test its sensitivities so that antibiotic therapy could be more specific. But blood-cultures taken during this 48 hours, and all subsequent blood-cultures, remained sterile. This suggested that the organism was highly sensitive to penicillin, and that 500,000 units given five times had been sufficient temporarily to sterilise her blood.

Course of the Illness

Penicillin was therefore given again in a dosage of 5 mega-units 8-hourly. After 5 days of this treatment her fever had subsided, and no new emboli had appeared.

On the 24th day, however, the fever returned and climbed to 101°F, and fresh petechiæ appeared in the skin. In view of this possible relapse streptomycin sulphate 1 g. twice daily was given in addition to the penicillin. 36 hours later an erythematous rash appeared on her back and on the extensor aspects of her limbs, and she had considerable pruritus.

Her temperature gradually settled to normal and her condition improved. Her W.B.C. which before streptomycin therapy had not been less than 7500 per c. mm., dropped to 4000–5000 per c.mm., with a normal differential count. Her hæmoglobin was never below 82% (12·1 g. per 100 ml.). Her rash persisted and the pruritus was partially controlled by antihistamines. Chlorpheniramine maleate ('Piriton') was given in a dosage of 4 mg. t.d.s. for 7 days, and was then replaced by a derivative of triprolidine hydrochloride ('Actidil') 25 mg. t.d.s. for 10 days.

On the 36th day her condition seemed satisfactory enough to warrant reducing the penicillin to 5 mega-units twice daily.

On the 41st day of her illness she developed an infection of the mouth and fauces which resembled thrush. The W.B.C. that day showed a total of 1000 per c.mm. with 34% neutrophils. In view of this evidence of severe granulocytopenia we reviewed her drugs to try to discover the cause. She had had penicillin and streptomycin with 0·5 ml. of 1% lignocaine ('Xylocaine') for each injection, pentobarbitone sodium ('Nembutal') gr. 3 at night, and the anti-histamines for the rash.

The streptomycin, lignocaine, pentobarbitone, and anti-histamines were discontinued, and prednisone therapy was commenced. 10 mg. was given on the first 2 days, 15 mg. on the 3rd, and 30 mg. on the 4th and subsequent days.

The lesions in the mouth and throat extended rapidly, but there was no rise in fever or deterioration in her general con-

dition. 2 days after the onset of the granulocytopenia the W.B.C. was 1300 per c.mm. with 6% polymorphs. The next day the pathologist reported that only scanty granulocytes were to be seen in the film, and that most of these were degenerate. This state of agranulocytosis continued for a further 3 days, no change being seen in the films.

The mouth and throat lesions were now static, and the patient showed no other signs of her defenceless condition. 7 days after the onset of the granulocytopenia the upswing occurred and the W.B.C. was 4500 per c.mm., with 51% polymorphs. The lesions in the mouth and throat cleared rapidly and she recovered steadily. The dosage of prednisone was reduced to 25 mg. for 2 days, 20 mg. for 14 days, 15 mg. for 3 days and 10 mg. for a further week, and then it was discontinued after nearly 5 weeks' treatment. The erythematous rash subsided slowly and finally disappeared a few days before the prednisone was stopped.

Penicillin was discontinued after 8 weeks and a total of 665 mega-units, and a week later the patient began to get up. Her convalescence was slow but uneventful; within 6 months she was driving her car. Apart from a little clumsiness of the right hand, slight ataxia of the right leg, and mild aphasia when excited, she had no remnant of her cerebral catastrophe.

There was no gross cardiac enlargement. The heart-sounds were normal. A third heart-sound with a "clicking" note was still present in early systole. The systolic ejection-type murmur, now softer, could still be heard over the whole precordium and it was loudest in the left 2nd–4th interspaces about 2 inches from the left sternal border. At no time was a diastolic murmur heard. A few months later she was screened by Dr. Ronald Jones who reported slight left ventricular enlargement and moderate uncoiling of the aorta. Her blood-pressure was 150/85.

Now—a year after her illness started—she is living a normal life.

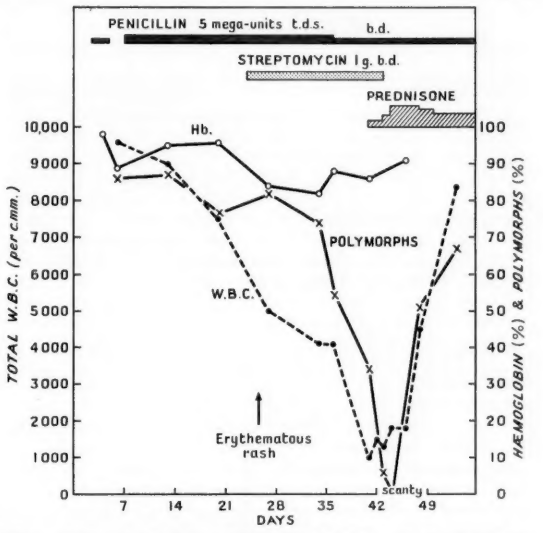
Discussion

Although it is tempting to regard both the endocarditis and the agranulocytosis as arising inexplicably and spontaneously in a previously healthy woman, it would perhaps be more reasonable to attribute the agranulocytosis to a leucotoxic drug. The endocarditis does not seem to have caused severe bone-marrow depression as the hæmoglobin never fell below 82%.

Agranulocytosis is commonest in middle-aged women, but none of the drugs which our patient was given is included as a cause in standard textbooks (e.g., Whitby and Britton or Wintrobe). At one time barbiturates were incriminated, but recent opinion has exonerated them (Goodman and Gillman 1955). Anti-histamines are known to cause agranulocytosis, and reports of several different members of this group causing granulocytopenia have appeared (Martland and Guck 1950, Bradlow 1951), but so far as we can discover neither triprolidine nor chlorpheniramine has ever caused agranulocytosis.

Lignocaine was used to make the injections less painful. About 1·5–2·0 ml. was given daily for 34 days before the agranulocytosis appeared. Granulocytopenia due to lignocaine has not previously been described, but a near relative—procaine amide—is known to cause it (Miller et al. 1951, Fabregoule and Messerschmitt 1954).

Our suspicions therefore fell upon the streptomycin. Evidence of drug sensitivity—an erythematous rash—developed within 36 hours of starting this antibiotic. Skin reactions to streptomycin are commonest after about a week of treatment, and the early appearance of a rash in this patient may indicate undue sensitivity. The patient had never previously had streptomycin. Agranulocytosis developed on the 17th day of streptomycin therapy, after a total dose of 34 g. The fall in the white-cell count and the number of polymorphs demonstrated (see figure) before streptomycin was given was probably due to the relative leucocytosis in the early days of the illness, and a gradual return to normal level as the infection came under control. The further fall immediately after exposure to streptomycin may have been due to a leucotoxic effect of the antibiotic.



The variations in the hæmoglobin, total W.B.C., and of polymorphs in relation to the antibiotics used.

Several reports have appeared of streptomycin causing agranulocytosis. The first description was in the Report to the Council on Pharmacy and Chemistry of the United States in 1947. Accounts followed by Feld (1949), Rossignol et al. (1949), Lereboullet and Oppert (1949), Oppenheim and de Meyer (1949), Wilder (1953), and Mahrer and Maret (1955). We think it would be reasonable to regard the streptomycin used in our case as the cause of the agranulocytosis.

Cortisone has revolutionised the treatment of agranulocytosis (Caldwell et al. 1950), and this is not now such a dreaded complication.

The association of endocarditis and agranulocytosis is rare, and we have found only two cases described previously (Russek et al. 1945, Krylov 1958). In the first case the agranulocytosis was caused by sulphadiazine used to treat subacute endocarditis, and in the second the agranulocytosis was rather vaguely attributed to the continued use of both streptomycin and penicillin.

We wish to thank Dr. Ronald Jones for his advice on the management of this case and for the screening examination; and Dr. A. B. Lintott, Dr. T. H. Shaw, and their staffs for ready cooperation with the pathological investigations.

REFERENCES

Bradlow, B. A. (1951) *S. Afr. med. J.* **25,** 945.
Caldwell, A. J., Adams, J. W., Anderson, J. E. C., Dick, A. A. (1950) *Canad. med. Ass. J.* **62,** 506.
Fabregoule, M., Messerschmitt, J. (1954) *Sang,* **25,** 510.
Feld, D. D. (1949) *Amer. Rev. Tuberc.* **59,** 317.
Goodman, L. S., Gillman, A. (1955) Pharmacological Basis of Therapeutics. London.
Krylov, A. A. (1958) *Sovetsk. Med. vost. Sib.* **22,** 144.
Lereboullet, J., Oppert, G. (1949) *Bull. Soc. méd. Hôp. Paris,* **65,** 997.
Mahrer, R. A., Maret, R. (1955) *U.S. Forces med. J.* **6,** 1193.
Martland, H. S., Guck, J. K. (1950) *J. Amer. med. Ass.* **143,** 742.
Miller, H., Pollock, R. C., Griffith, G. G. (1951) *J. Lab. clin. Med.* **38,** 850.
Oppenheim, M., de Meyer, G. (1949) *Schweiz. med. Wschr.* **79,** 1187.
Report to the Council on Pharmacy and Chemistry (1947) *J. Amer. med. Ass.* **135,** 634.
Rossignol, G., Rousselin, L., Perrin, L. F. (1949) *Bull. Soc. méd. Hôp. Paris,* **65,** 370.
Russek, H. I., Smith, R. H., Zahman, B. L. (1945) *Ann. intern. Med.* **22,** 867.
Whitby, L. E. H., Britton, C. J. C. (1957) Disorders of the Blood. London.
Wilder, R. (1953) *Tubercle, Lond.* **34,** 163.
Wintrobe, M. M. (1956) Clinical Hæmatology. London.

New Inventions

RECORDING PORTAL VENOUS PRESSURE IN MAN

IN this paper I describe a method by which can be made continuous recordings of portal venous pressure in man, both during and after operations for the prevention of hæmorrhage from œsophageal varices. In the past 9 months it has been used on twenty-three patients, having now become a regular accompaniment of decompression procedures, such as porta-caval anastomosis, and of venous disconnection operations, such as gastric transection. The method is simple, and has not caused either morbidity or mortality.

TECHNIQUE

At operation, one end of a polyvinyl chloride (P.V.C.) cannula of internal diameter 2 mm., and length 10 cm., is tied into an omental vein or the left gastroepiploic vein. The other end of the cannula is connected by P.V.C. tubing taken from standard infusion sets in use in the hospital, to a saline manometer carrying a hollow vulcanite float, a wire, and an ink pen which writes on a paper-covered kymograph.

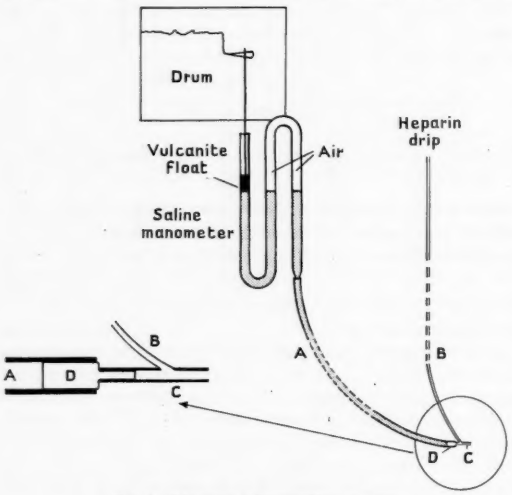


Fig. 1—Diagram of recording system.
A=standard P.V.C. tubing, B=side-limb, C=cannula, D=stainless-steel link connecting C to A.

To prevent coagulation of any blood entering the recording system, the cannula has a side-limb (internal diameter 0·5 mm.) which carries a solution of heparin (2500 i.u. per litre normal saline at 10 drops per minute) into the recording system. This prevents coagulation in the cannula without affecting the patient's clotting-time.

So that the wide range of pressures in patients with portal hypertension may be recorded easily, an air-lock is provided in the manometer (see fig. 1). As a result, when the pressure in the portal system changes by 10 mm. saline, it is recorded as 3·33 mm. on the kymograph. Because the wire on the float is 30 cm. long, a range of pressure variation of 0–999·9 mm. is obtainable on the drum, which is 30 cm. deep.

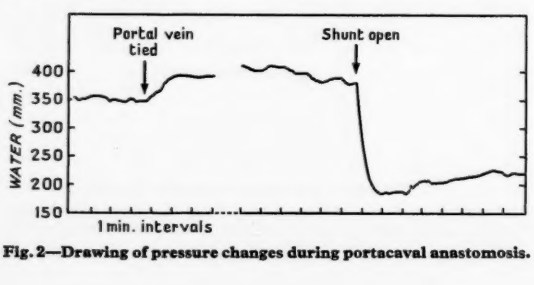


Fig. 2—Drawing of pressure changes during portacaval anastomosis.

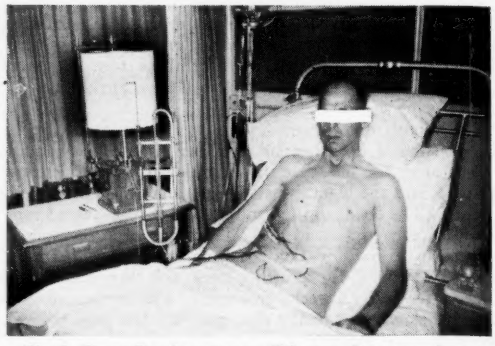


Fig. 3—Recording in progress 48 hours after operation.

At the end of operation, the tubing is brought out through one end of the incision in the parietes, and thus is left in situ. Before removing the cannula, 1–5 days after operation, the tubing is clamped off for 24 hours and then gently pulled out.

RESULTS

Details will be published later of the results of these recordings, their variation with operative procedures, and the changes induced by vasomotor drugs. Fig. 2 shows the changes during the operation of portacaval anastomosis on a patient with cirrhosis of the liver and portal hypertension. Fig. 3 shows a recording in progress 36 hours after portacaval anastomosis.

The double-lumen cannulæ are manufactured by Portland Plastics, Ltd., Hythe, Kent. The floats and ink-writing system are obtainable from C. F. Palmer Ltd., Brixton, London. The P.V.C. connector tubing is from disposable recipient sets made by Capon Heaton and Co. Ltd., Birmingham.

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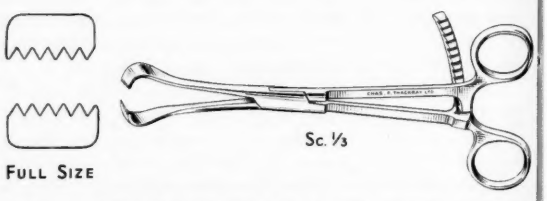
BONE-FRAGMENT FORCEPS

IN the course of an orthopædic operation the need often arises to remove a fragment of bone which is either firmly attached to soft tissues or loose but inaccessible. The fragment must be held and traction exerted while the soft tissues are dissected from it. But, because most sequestrectomy forceps or bone-holding forceps are not shaped to grip irregular fragments and their handles do not lock the operator's hand tires in the attempt to grip and pull on the forceps.



The forceps shown here overcome this problem. The jaws have teeth that will hold firmly on to any bone fragment, and, with the handles closed, traction can be exerted easily. There are two sizes, for large or small fragments of bone.

The forceps are available from Messrs. Chas. F. Thackray, 10, Park Street, Leeds, 1.

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AN ARTERY BANK

PRESERVATION and storage of homologous artery grafts present difficulties in smaller centres without facilities for freeze drying. Methods involving electrical deep-freeze apparatus and " dry ice " are expensive, and often give inadequate space for storage of large tube containers. The bank container shown here is the result of an attempt to overcome some of the problems, and it was built by Mr. C. S. N. Swan, M.R.C.O.G., for use in the hospitals of the South Warwickshire Group. The bank comprises outer and inner ' Perspex ' boxes, with the space between completely filled with glass wool. The outer box measures 44×28×38 in. externally, and the space is 7 in. across. Wooden blocks are temporarily inserted to

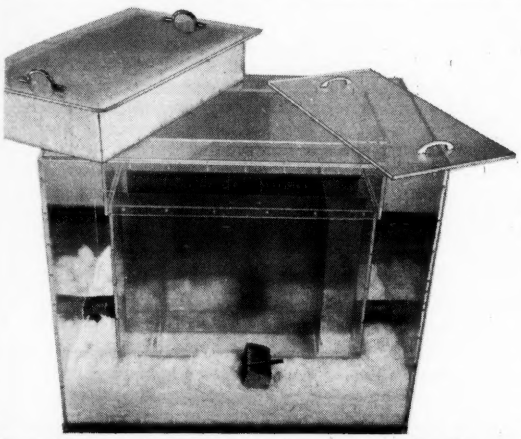

Fig. 1.—Bank partly packed with glass wool, showing the construction of the two perspex boxes.

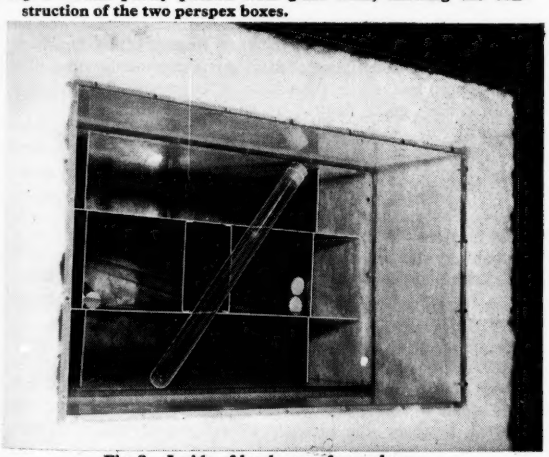

Fig. 2.—Inside of bank, seen from above.

maintain the position of the inner box during packing with glass wool (fig. 1). A low temperature (−75°C to −80°C) is maintained by dry ice contained in the outer and central compartments of the inner box, which is divided by a metal baffle (fig. 2).

Tests have shown that the required temperature is adequately maintained in the bank. The cost per annum of the perspex is about £90, and of the dry ice about £130. The dry ice must be replenished twice weekly under normal conditions, and three times weekly in hot weather. A smaller model of this bank, measuring 22×22×26 in. has been used and found satisfactory in this hospital group for the past four years, its only disadvantage being that the diameter and length of the glass graft-storage tubes is severely limited.

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Reviews of Books

Clinical Physiology

Editors: E. J. M. CAMPBELL, B.SC., PH.D., M.D., M.R.C.P., assistant, department of medicine, Middlesex Hospital; C. J. DICKINSON, B.A., B.SC., B.M., M.R.C.P., Leverhulme research scholar, Middlesex Hospital Medical School, London. Oxford: Blackwell Scientific Publications. 1960. Pp. 530. 50*s*.

THIS book, covering a great deal of ground and written by a number of experts, will inevitably be judged by two standards. On the one hand, a reader may study those subjects with which he is himself most familiar and he may feel aggrieved because certain things are omitted. On the other hand, he may consider those parts of the book where his own knowledge is general rather than particular, and criticism from this standpoint is probably more useful, since the book is meant for the non-expert.

The book should be particularly helpful to undergraduates entering on their clinical training, and it might even be recommended for use at the end of the preclinical period. Its importance lies in the fact that in each section, side by side, it summarises certain aspects of both physiology and medicine, thus emphasising the close relationship between the two. The sooner medical students realise that patients deserve something other than empirical treatment the better. It is common experience that in the final years students lament their earlier lack of attention to physiology.

Because of its immensity, neurology has been omitted. The other body systems are considered from four aspects—normal and disordered function, the physiological bases of tests used, and how the information obtained can be used in diagnosis and assessment. At the end of each chapter a few useful references are given as a starting-point for further reading. If they have any time for reading, general practitioners will find the book a useful summary of the newer theories and of the tests to which their patients may be subjected when they vanish into hospital " for investigation ". Recent graduates can use it as a reminder of things only too easily forgotten. We hope that in their eagerness to be scientific clinicians they will not subject their patients to all the tests, but will realise how often sound observation combined with a few carefully chosen tests will suffice to clinch a diagnosis, thus sparing the patient and saving time and money.

This book is concise and easy to understand, and offers much basic information. It should be popular.

Surgery in World War II

Neurosurgery. Vol. 2. Prepared by Major-General S. B. Hays, surgeon general, U.S. Army. Editor in chief: Colonel J. Boyd Coates, Jr., M.C., Medical Department, United States Army. Washington: Office of the Surgeon General. 1959. Pp. 705. $7·00.

THIS is an important record of organisation and achievement. During the late war there were wonderful advances in the treatment and rehabilitation of those with wounds of the spinal cord, and this volume describes the important contributions made by American surgeons to this subject.

Wounds of peripheral nerves were handled by neurosurgeons in the American Army, and they clearly organised an impressive service. For the clinical record the strength of separate muscle groups was recorded by using spring balances rather than by the 0–to–6 code used in Britain. This is probably the best method for the later stages of recovery but not so good for the early flickers of movement which are looked for when a nerve has been sutured. The techniques of examination, however, were scientifically applied, and when functional conduction was in doubt the effect of blocking the uninjured nerves with local anæsthetic was used. The discussion of the causes and treatment of causalgia is interesting; and the technical aspects of nerve suture and nerve grafting will be studied by those interested in the subject.

In the treatment of nerve injuries there is a danger that the patient may spend many demoralising months in hospital

or convalescent home waiting for a nerve to regenerate. In order to counter this, a 90-day work-furlough plan was introduced which enabled these patients to take up work for a substantial period of time. Certainly all who have dealt with nerve injuries will be aware of the bad effects of idleness on these patients, and of course most nerve injuries are compatible with very full activity of one kind or another without serious handicap to a regenerating nerve.

The Purpose and Practice of Medicine

Selections from the writings of Sir James Spence. Edited by members of the child-health department, King's College, Newcastle upon Tyne, with the technical assistance of P. B. DUREY, B.A., A.L.A. London: Oxford University Press, for the University of Durham. 1960. Pp. 319. 42*s*.

THE publication of this selection of writings and addresses by the late Sir James Spence is an apt tribute to a great physician and a wise counsellor. His broad independent mind had a profound influence on the rapidly evolving social and medical scene which followed the late war.

The introductory memoir, really a miniature biography, by his lifelong friend and colleague Sir John Charles, is a vivid and penetrating sketch which will charm all readers and greatly enhance their understanding of the following anthology.

The twenty papers and addresses which have been selected are arranged in five sections—The Nature of Disease, The Study of Disease, Children and Families, The Care of the Sick Child, and The Practice of Medicine and the Training of Doctors. His lectures on The Purpose of the Family, The Care of Children in Hospitals, and The Need for Understanding the Individual are of the very essence of his philosophy and humanity, which made a deep impression on all who met him, particularly the many young pædiatricians who were privileged to work with him in Newcastle.

Textbook of Otolaryngology

DAVID D. DEWEESE, M.D., clinical professor of otolaryngology, University of Oregon Medical School; WILLIAM H. SAUNDERS, M.D., associate professor of otolaryngology, Ohio State University College of Medicine. St. Louis: C. V. Mosby. London: Henry Kimpton. 1960. Pp. 464. 65*s*.

THIS textbook is written for the medical student and general practitioner, and covers the whole of ear, nose, and throat diseases in a surprisingly small space. Additional references are provided at the end of each chapter. The text is clear, well set out, and generously illustrated. Several laryngeal conditions are documented by Holinger's internationally famous photographs, giving an accurate picture of the commoner clinical appearances in a region which the student may find difficult to examine. Emphasis is properly laid on the management of common conditions. Tonsils and adenoids, sinusitis, nosebleeds, and otitis media are dealt with in adequate detail. Malignant disease is not discussed so well as some other subjects and the introduction of lymphoepithelioma as a group will not appeal to British readers. The bias of the book is naturally towards American practice, with emphasis on local anæsthesia for most operations and preference for surgery rather than radiotherapy for most carcinomas. The concluding chapters on speech problems, rehabilitation of the deaf, the facial nerve, and the salivary glands are very useful.

Henry E. Sigerist on the History of Medicine

Editor: FELIX MARTI-IBANEZ, M.D., professor and chairman, department of the history of medicine, New York Medical College. New York: M.D. Publications. 1960. Pp. 313. $6·75.

IN 1947 Dr. Henry Sigerist resigned from his chair at Johns Hopkins University, where he had succeeded William H. Welch with such distinction, and retired to Switzerland. There, surrounded by his library of some 15,000 volumes, he devoted himself to writing a history of medicine, which might well have been the most notable work of its kind ever produced. Unfortunately, he was hampered by ill health, and when he died, in 1957, only two of the eight volumes he contemplated had been finished.

Yet, as Dr. Marti-Ibanez points out in a preface to this anthology, in one sense Sigerist did complete his task; for his many lectures and articles dealt with every aspect of the subject, and would, arranged chronologically, cover almost all of it. This book, however, is not an attempt at such an arrangement, but a selection of Sigerist's writings, which he himself made. It gives an admirable picture of his enthusiasms, and of the breadth of intellect with which he pursued them. There are half a dozen essays on medical history generally, and five more on the medieval period which was his forte. The subsequent chapters on the Renaissance include an account of how Paré treated burns with onion juice four hundred years before an antibiotic agent was demonstrated in it, and another of the development of American medicine after the founding of the first medical school at Philadelphia in 1765. Finally, there are six articles, around, rather than about, Sigerist's main interests. These are reminiscent of several which Osler wrote, and they are intriguing because they give some insight into the way he lived and worked. It will come as no surprise to those who are familiar with his writings to learn that every day he read five newspapers in four languages; or that when he spoke of his "small library next to my bed" of favourite books, he was referring to a collection of 500 volumes.

Tomorrow Will be Sober

LINCOLN WILLIAMS. London: Cassell. 1960. Pp. 208. 15*s*.

Dr. Williams sets out to present the problem of the alcoholic to non-medical people who, through their work or family, may have to meet it. The background, development, symptoms, medical and psychiatric complications, treatment, and outcome of alcoholism are described, together with the effects and mode of action of alcohol. He gives a realistic but sympathetic picture of alcohol addiction, illustrated by several case-histories. The different forms of treatment are discussed, with a proper avoidance of particular recommendation but with emphasis on the role of Alcoholics Anonymous. There is also a particularly good chapter by an Irish founder-member on the work of this organisation. It is emphasised that little good can come from forcing treatment on an alcoholic before he is prepared for it (not usually until he has reached his rock-bottom), but sensible advice is given on how to help at all stages. Sermonising is useless, as are empty promises of cure: what he needs is hope together with a firm appraisal of what is required and what can be done. The excessive drinker is rightly distinguished from the addict, and for the latter the aim must be total abstinence. Rev. Frederick Read discusses spiritual aspects.

Some readers may disagree with the emphasis at times (many would not give hypnosis much of a place in therapy) and the description of alcoholic personalities (the good, sad, mad, and bad) is an oversimplification but perhaps a useful one. In general, however, the problem is well represented, the book is readable (though sometimes rather wordy), and it can certainly be recommended.

Body Fluids in Surgery (2nd ed. Edinburgh: E. & S. Livingstone. 1960. Pp. 276. 21*s*.).—The second edition of this valuable work by Prof. A. W. Wilkinson has lost none of its original clarity though much has been revised and rewritten; moreover the abundance of information in no more than 250 pages is an achievement made possible by Professor Wilkinson's command of English. In the four years since the first edition much has been added to the literature on the subject. This he has assimilated, but perhaps the most important development is his adoption of the convention that an acid is a substance which yields hydrogen ions and a base, whereas a base combines with hydrogen ions to form acid. In this, as elsewhere, he leads the way.

THE LANCET

LONDON 30 JULY 1960

Artificial Insemination

IN this country the number of children conceived as a result of artificial insemination with a donor's semen (A.I.D.) is probably just over a hundred a year. Although the practice is increasing—the number of such conceptions has apparently doubled in the past decade—and may further increase as a result of recent publicity, the number of children born in this way is not likely to reach significant proportions in the foreseeable future. Even if A.I.D. were to increase twentyfold, a marriage between children of the same donor would be unlikely to occur more than once in fifty to a hundred years.

In the great majority of cases, A.I.D. is used because of sterility or gross infertility in the husband. Very occasionally it is undertaken for other reasons—for instance, where the husband has severe hereditary disease or where there is rhesus incompatibility. According to evidence given to the departmental committee whose report was published last week,[1] A.I.D. is undertaken in this country only if both husband and wife agree, and even then only after careful consideration. " The practitioner tries to establish not only that the child is likely to have a secure material background, but also that the marriage is likely to remain stable and harmonious; that husband and wife are entirely suited in personality and temperament to have a donor child, and aware of the responsibilities they are undertaking. " Practitioners occasionally receive inquiries from single women but never proceed. Notwithstanding some suggestions to the contrary, the departmental committee's report indicates that the practitioners and the couples concerned behave with a due sense of responsibility.

What, then, should be society's attitude towards donor insemination—encouragement, tolerance, or disapproval? On this issue the committee was divided. None of its members favours A.I.D. for single women, widows, or wives separated from their husbands, or for married women without the husband's consent; and the majority believe that, even with the husband's consent, A.I.D. is an undesirable practice and should be discouraged as " an offence against society " and as " most unwise and a grave injustice . . . to the intended child ". They do not wish to make it a criminal offence, which they would regard as dangerous. They would place it in the category of conduct which, although regarded by the community as immoral, should not be classed as criminal and therefore punishable by the State. The minority, though not in favour of encouraging A.I.D., maintain that it may properly be employed in small numbers of cases provided that the marriage is stable and both applicants and donors are carefully and expertly selected. In such cases A.I.D. should not be classed as discreditable, and the children should be regarded by the law as legitimate. Both the majority and the minority propose only minor legal changes, and on most of these the committee was unanimous: for instance, that the acceptance of donor insemination without the husband's consent should be a ground for divorce. The absence of proposals for controversial legislation should encourage reasoned discussion of this difficult problem.

Are the majority justified in so strongly condemning the practice of donor insemination? They appear to have the support of many doctors as well as of religious bodies and other organised opinion. None the less, some of the objections seem to be concerned with risks to be considered by a couple contemplating A.I.D. rather than with matters of principle. No doubt, the reception by the wife of the seed of another man may give rise to emotional difficulties, and either husband or wife may later regret the birth of an artificially conceived child. But this is no more a question of principle than is the possibility that a couple may subsequently regret their decision to adopt a child. And, while the committee properly draws attention to the needs and rights of the intended child, too much can be made of the risks. The majority are in effect saying that it were better for the child not to have been born than for it to run the risk of emotional disturbance on learning of its A.I.D. origin.

The majority do, however, raise a question of principle in considering whether A.I.D. is compatible with the sanctity of marriage. They see clearly enough—which has not been apparent to some commentators—that donor insemination and adultery are poles apart; but that, as in adultery, the wife receives the seed of a man other than her husband they evidently regard as a fatal objection. " To many this is a decisive argument against A.I.D. Even though its effects on the marriage were in all cases wholly good, it would go against what has hitherto been regarded as the essential nature of marriage." This is to enter the realm partly of theology and partly of the ingrained attitudes of society at large. The technique of insemination is still so new that the attitudes of both theology and society may change as the issues are further debated. For, as the majority report recognises, the history of the institution of marriage shows that the main threat to the physical side of the union has always been adultery and that the undertaking, given at marriage, to " forsake all other " is primarily an undertaking to refrain from adultery.

The practice of A.I.D. must of course place a heavy responsibility on the doctor. He can hardly escape advising the couple as to the desirability of their seeking a child by this means; and, if artificial insemination is undertaken, he will have to choose the donor. The majority report suggests that in many respects the practice of A.I.D. is beyond the proper jurisdiction of a doctor, and it names this as another reason for disapproving of donor insemination. On the other hand, it can be argued that the doctor may decide whether he is prepared to accept this responsibility.

Whether or not one agrees with its conclusions, this is

1. Report of the Departmental Committee on Human Artificial Insemination. Cmnd 1105. H.M. Stationery Office. 5*s*. 6*d*.

a valuable report which should stimulate discussion. It would be unfortunate if the subject were quietly put aside because it involves only a tiny fraction of births. In the United States A.I.D. is apparently more widely practised,[2] and in this country the demand is quite likely to increase. A clear medical and public opinion is therefore desirable.

Healing of Wounds

MUCH time, thought, and investigation have been devoted to the healing of wounds. Professor DUNPHY,[3] in a Moynihan lecture, has sifted out material of value to the surgeon. He emphasises the importance of considering the various components of repair—epithelialisation, contraction, connective-tissue growth, and repair of specialised tissues—as separate though interrelated biological processes of which one may be retarded by physical or chemical agents while the others proceed normally.

In incised wounds the epithelium does not merely bridge the gap but grows down to the deeper structures, where it proliferates irregularly and, only after collagen fibres appear, regresses to be arranged in a normal pattern.[4 5] DUNPHY suggests that this interplay between the epithelium and connective tissue simulates the initial and regressive phases in neoplasia. But there are at least two further analogues: in chronic ulcers of the skin the epithelium at the edges shows much irregular proliferation and interplay with the deeper tissues and sometimes becomes malignant (Marjolin's ulcer); and in chronic peptic ulcers the epithelium at the edges undergoes very irregular hyperplasia, and sometimes considerable extension into the tissues at the base, making the development of malignancy very difficult to determine.

DUNPHY points out that contraction (which is to be distinguished from contracture) is greatest on the back of the neck, the back, the abdomen, and buttocks, and least on the extremities and the front of the chest and neck, and in all burn wounds (where early grafting is required). The exact force causing contraction is not known; but some part of it resides in a narrow edge of tissue round the wound periphery [6] and there is apparently also a centripetal force from without this area.[7] WATTS [8] has shown that wound contraction is independent of epithelial regeneration and of growth of granulation tissue and is most effective at right-angles to Langer's lines [9] of skin tension: the most rapid healing is obtained by planning the wound to make best use of these tension lines; but, unless the edges of the wound are brought together by sutures, healing will probably never be satisfactory.

The healing of a wound or gap in the tissues is conditioned by the rate of growth and strength of the connective tissue which fills the gap. DUNPHY points out that our knowledge of many of the factors concerned in this process rests on measurements of the tensile strength of sutured wounds. From three or four days after the wound is made the tensile strength increases rapidly until about the fourteenth day and then very gradually for up to a year. DUNPHY declares that the deleterious effect on the healing process of vitamin-C deficiency and protein starvation depends entirely on their timing: if there is no deficiency at the time of wounding, repair will proceed normally even if the deficiency develops later. Similarly, cortisone in large doses depresses the formation of collagen only if healing has not started. Immediately after total-body irradiation, healing proceeds normally, but it may be impaired later because of bleeding from hypoprothrombinæmia.

Apart from these " outside " factors, the initial three to four days' delay in development of tensile strength is of great interest to surgeons. Originally thought to be a lag phase related to demolition and reorganisation in the wound,[10] this interval is regarded by DUNPHY as preparative, since fibroblastic activity follows very quickly after the injury. Many topical agents have been applied in efforts to hasten this or later stages, but quantitative studies indicate that they merely restore impaired healing to normal. This has been shown in another way by WALLACE,[11] who advocates biological covers (plasma pellicle, eschar, or skin graft) and a return to Lister's principle of complete desiccation of wound discharge and an outer protective antiseptic bandage. Beyond doubt a resutured wound heals more rapidly than a fresh primary wound,[12] chiefly owing to the absence of the so-called lag phase: this phenomenon persists and can be used for up to a month, though it is most prominent in the first fortnight. With the aim of shortening the preparative phase DUNPHY has administered bacterial pyrogens, which he finds lead to more rapid formation of collagen. Administration of histamine before wounding and during healing was shown by BOYD and SMITH [13] to be associated with more rapid and firmer wound healing, judged both histologically and by measurement of tensile strength; while similar administration of compound 48/80, a substance which lowers the histamine content of the skin, retarded healing. Professor KAHLSON [14] believes that the effect of histamine on regenerating tissue is due not simply to the histamine content but to the histamine-forming capacity (H.F.C.) of the tissue concerned. He and his colleagues show on p. 230 of this issue that skin and granulation tissue have a relatively low content of histamine, yet have a very high H.F.C.: the histamine is not stored locally but is either used up or carried elsewhere. In female rats to which radioactive histidine was administered, they measured the formation of endogenous histamine (as opposed to the use of dietary histamine). The H.F.C. of the skin was raised and the histamine content lowered by compound 48/80 or polymyxin B

2. Williams, Glanville. The Sanctity of Life and the Criminal Law; p. 111. London, 1958.
3. Dunphy, J. E. *Ann. R. Coll. Surg. Engl.* 1960, **26**, 69.
4. Hartwell, S. W. The Mechanisms of Healing in Human Wounds. Springfield, Ill., 1955.
5. Gillman, T., Penn, J., Bronks, D., Roux, M. *Brit. J. Surg.* 1955, **43**, 141.
6. *Lancet*, 1958, ii, 1165.
7. Billingham, R. E., Medawar, P. B. *J. Anat., Lond.* 1955, **89**, 114.
8. Watts, G. T. *Brit. J. Surg.* 1960, **47**, 555.
9. Kraissl, C. J. *J. plast. reconstr. Surg.* 1951, **8**, 1.
10. Howes, E. L., Scoy, J. W., Harvey, S. C. *J. Amer. med. Ass.* 1929, **92**, 42. Howes, E. L., Harvey, S. C., Hewitt, C. *Arch. Surg., Chicago*, 1939, **38**, 934.
11. Wallace, A. B. *Scot. med. J.* 1960, **5**, 279.
12. Savlov, E. D., Dunphy, J. E. *Surgery*, 1954, **36**, 362.
13. Boyd, J. F., Smith, A. N. *J. Path. Bact.* 1959, **78**, 379.
14. Kahlson, G. *Lancet*, 1960, i, 67.

administered for three days and discontinued before the wounding; and in subsequent test wounds the tensile strength was 20% greater than that in controls. When the H.F.C. was lowered by administering the enzyme-inhibitor, semicarbazide, and a diet deficient in pyridoxine (depriving histidine decarboxylase of its coenzyme), the healing of test wounds was grossly retarded: when the two depressing elements were corrected, the H.F.C. showed a characteristic "overshooting phase" with increase in tensile strength 53% above normal.

The full significance of this work is not yet apparent, but it may lead us to some means by which preoperative preparation hastens healing. This effect may have been produced in the work of YOUNG et al.,[15] whose findings were fully confirmed by SANDBLOM and MUREN.[16] Both groups reported that a recently healed primary wound accelerated healing of a secondary wound, the former group suggesting that this was due to a "wound hormone", and the latter that the effect was due to the previous shaving and preparation of the site of the second wound.

Transfused Blood and Cardiac Arrest

CARDIAC arrest is rare in major surgical operations, but its incidence seems to vary considerably from centre to centre. Sometimes a clear explanation, such as a cardiac infarction, can be found; but often no obvious cause is detectable even at necropsy.

LE VEEN [17] having reviewed his experience, finds that massive blood-transfusion underlay cardiac arrest in 68 of 157 cases; and he puts forward sound arguments for the hypothesis that the critical factor is the ratio of potassium to calcium in the venous return to the heart: should this ratio become excessively large, cardiac arrest will follow. The potassium content of the mixed venous blood returning to the auricle may be very different from that of blood obtained from the peripheral veins; for into the vena cava drains the blood returning from the liver, and the liver contains the most labile pool of potassium in the body. From the liver, potassium is released by many different stimuli—anoxia, carbon-dioxide retention, and adrenaline whether injected or released from the adrenal medulla in response to hæmorrhagic shock. Furthermore in hæmorrhagic shock in dogs the minimum lethal dose of potassium injected intravenously may be reduced by a third. LE VEEN declares that even these powerful factors are not the only ones to consider, for massive transfusion of ice-cold blood may chill the heart and great vessels to so low a temperature that they feel like cold metal to the touch: such temperatures must disturb the normal control of the heart-beat.

LE VEEN has serious trouble with his supply of blood for transfusion; only 57% was less than thirteen days old (compared with 69% in a sample check on blood in a British hospital). His observations on the diffusion of potassium out of cells of stored blood indicate that some 40% of the blood transfused contained more than 23 mEq. of potassium per litre—about five times the physiological level.

The lessons seem to be clear. Firstly for the anæsthetist, the most useful warning sign of a raised venous potassium level, and thus of possibly impending cardiac arrest, seems to be a rise in venous pressure; and anoxia and hypercapnia greatly increase the probability of a raised potassium level. As reduction in blood-volume must be avoided, bleeding should be continuously adequately compensated by transfusion (a procedure which would be facilitated by continuous monitoring [18] of blood-loss); and, especially when massive transfusions are given, the effect of citrate in increasing the potassium/calcium ratio should be offset by frequent injections of a calcium salt into the vein of another limb. Secondly, for the transfusionist, fresh blood is needed if massive transfusions are to be successful; if really fresh blood is not available, then intra-arterial may prove to be preferable to intravenous transfusion; and if massive transfusion is expected, and the blood must be infused intravenously rather than into an artery, the blood should perhaps be held at room temperature instead of in a refrigerator, and the patient digitalised before operation. Finally, since adrenaline releases potassium from the liver, its administration should be replaced by that of isoprenaline, which does not have this action and is a more effective cardiac stimulant. It would be interesting to monitor continuously the electrocardiographic changes during a difficult and bloody operation, or even during replacement of blood after recurrent hæmorrhage.

15. Young, J. S., Fisher, J. A., Young, M. *J. Path. Bact.* 1941, **52**, 225.
16. Sandblom, P., Muren, A. *Ann. Surg.* 1954, **140**, 449.
17. Le Veen, H. H., Pasternack, H. S., Lustrin, I., Shapiro, R. B., Becker, E., Helft, A. E. *J. Amer. med. Ass.* 1960, **173**, 770.
18. Le Veen, H. H., Rubricius, J. L. *Surg. Gynec. Obstet.* 1958, **106**, 368.
19. Report of the Maternity Services Committee. H.M. Stationery Office, 1959.
20. Adamson, T. L., Brown, R., Myerscough, P. R., Loudon, J. D. O. *J. Obstet. Gynæc. Brit. Emp.* 1960, **67**, 243.
21. Stabler, F. *Proc. R. Soc. Med.* 1949, **42**, 9.

Annotations

THE OBSTETRIC FLYING-SQUAD

THE obstetric flying-squad, from small beginnings twenty years ago, has spread to all parts of this country. Several hundred women owe their lives to this service and it has saved thousands more from chronic ill health. The need for such an emergency service is likely to continue for years in view of the recommendation by the Cranbrook Committee [19] that the domiciliary-confinement rate should be 30%.

In a review of the Edinburgh emergency obstetric service Adamson et al.[20] report their results over the ten-year period 1948–57. Most calls were answered by registrars accompanied by a sister and a house-surgeon. Of the 403 cases attended, 3 women died before and 2 after the squad's arrival. In the circumstances these are excellent results and reflect great credit on all concerned. In Newcastle, by contrast, the flying-squad has always been staffed at a more senior level.[21] Calls are taken usually by a consultant obstetrician, and only occasionally by a senior registrar; for several years a consultant anæsthetist has gone out on all calls.

Each community has its own particular traditions and circumstances, and it is not surprising that the staffing and organisation of flying-squads vary between one

region and another. Where short distances are travelled and few calls are received, there is understandably a tendency for the flying-squad to become a resuscitation service run by junior staff and for patients to be brought back to hospital. Where there are long distances to travel and serious intrapartum as well as postpartum complications are met (as in Newcastle) there is need to send out experienced personnel who can deal safely with any emergency in the home.

Unless a skilled anæsthetist is present it is wise to keep to the simplest of anæsthetic techniques with a minimum of equipment. Chloroform has been used widely and is still favoured by the Edinburgh squad. It is easily transported, is non-inflammable, and quickly gives excellent relaxation for any intrauterine manipulation. Provided the dangers associated with the use of this anæsthetic are appreciated there is much to be said in its favour. Many general practitioners, through their domiciliary maternity work, have become skilled in the use of chloroform and also of open ether. There is no evidence to suggest that the anæsthetic techniques in domiciliary practice are contributing to maternal mortality. Of 1410 maternal deaths in England in 1952–54 only 2 were attributed to anæsthesia in the patient's home.[22] In Newcastle, with an experienced anæsthetist available, transportable lightweight machines delivering nitrous oxide, oxygen, and trichloroethylene are used. For most cases this mixture is adequate, but a little ether can be added if necessary; a shovelful of sand or earth, or a wad of cottonwool soaked in water, will damp down any open fire.

The flying-squad service, admirable in many ways, is a constant reminder of the dangers inherent in domiciliary obstetrics. In a real emergency, delay of half to one hour in the arrival of blood and skilled assistance may mean death for the mother. Careful selection of cases for home delivery and better medical and nursing care should reduce the number of flying-squad calls. There is, however, no evidence that such a reduction is being brought about: indeed, the number of calls is increasing steadily in some areas. Efficient flying-squad cover may give general practitioners and domiciliary midwives a false sense of security and encourage them to book for home confinement cases which should be referred to hospital. This disturbing possibility should be carefully examined. The reason for each call should be assessed critically, objectively, and frankly. This information would lead to a better understanding of the real need for an obstetric emergency service and could be most helpful in planning for the future.

22. Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1952-54. H.M. Stationery Office, 1957.

P.P.L.O.

THE medical bacteriologist does not devote much attention to the pleuropneumonia-like organisms. Organisms of the eponymous species (now known as *Mycoplasma mycoides*) isolated by Nocard in 1898 are about the size of the larger viruses. They will not grow on the media commonly used in diagnostic bacteriology, but unlike viruses and rickettsiæ can flourish extracellularly. They must be recognised by their colonial appearances alone and any classification is difficult. Some are saprophytes but others undoubtedly cause disease in some animals. The part they play in human disease is open to argument. They occur quite commonly in the genital tract of both sexes, and, like some other organisms living on the mucous surfaces, occasionally cause local or systemic infections.[1] The attempt to associate them with "non-specific urethritis" has not been very successful; and it would not be far wrong to say that inflammation of the genital tract from any cause—gonococci, trichomonas, or yeasts—encourages their detection. We would know much more about P.P.L.O. if methods suitable for their cultivation were applied to all routine material coming to the laboratory; but this would involve a great deal of work.

During the past few years P.P.L.O. have joined the ranks of the laboratory pests. Those who grow viruses in tissue culture know very well that from time to time a murrain strikes the sheets of embryonic or malignant cells in which they hope the viruses will flourish. Some observant fellow spotted that this accident is often associated with, or even caused by, infection with a strain of P.P.L.O. Since the tissue cultures are bathed in a fluid containing penicillin to prevent bacterial contamination, they provide a suitable culture medium. It has been customary to attempt to kill off the P.P.L.O. with chlortetracycline, but Hayflick has shown that the same effect may be obtained by holding the infected tissue culture at 40°C for twelve to eighteen hours. If this is confirmed it will be a useful short cut.

The study of P.P.L.O. has been complicated by another factor. Almost since the dawn of bacteriology claims have been made for the existence of filterable forms of pathogenic bacteria. Some of these yarns were without doubt due to poor technique and a desire for lasting fame, but during the past twenty years it has become clear that such filterable forms will develop in the laboratory—especially if the parent is treated with penicillin. These are the so-called L forms, and in many ways they are very like P.P.L.O. Neither seems to have any internal structure. Both are soft and fragile: if a staphylococcus is a tennis-ball, an L form is a tuft of candy floss. The colonies on solid media are similar. Both are resistant to penicillin, and the growth of both is inhibited by antibodies without complement. L forms do not grow as easily as P.P.L.O., but a more essential difference seems to be that L forms have never been found in Nature: they are no more than laboratory artefacts. Until recently L forms were not thought to be pathogenic, but this may have been an error. The obvious question is whether P.P.L.O. are the L forms of bacteria which we may know by some other name. There is some evidence that this is true of the saprophytic species but not of those which have been identified as causing disease.

In time the medical bacteriologist will get round to looking for these organisms. The literature he will find to be scattered and somewhat obscure, but he will find all that he will want to know in the report of a conference held last year and now published.[2] It is a model of what such a report should be. The papers are short but the illustrations lavish. The discussions are reported fully and without too much editorial tidiness. It would be thankless to discuss the papers individually, but the contributions of D. G. ff. Edwards are outstanding. He seems to have led the conference firmly but gently, so that readers of the report can not only add much to their knowledge but get a picture of some interesting and fruitful debates.

1. Stokes, E. J. *Lancet*, 1955, ii, 276.
2. Biology of the Pleuropneumonialike Organisms. *Ann. N.Y. Acad. Sci.* 1960, **79**, 309.

THE HIDDEN BLEEDING-POINT

MASSIVE gastrointestinal bleeding may arise from obscure causes—aneurysm of the hepatic artery [1] for one, duodenal diverticulum [2] for another—but the source of bleeding from even the commoner causes may baffle the surgeon. This difficulty led Langrall et al.[3] to undertake a pathological evaluation of patients who had died of massive hæmorrhage at the Mayo Clinic between 1944 and 1955. These accounted for 135 out of 7312 necropsies, and almost 75% (93) of the hæmorrhages were due to peptic ulceration (50) or œsophageal varices (43). 15% (20 cases) were due to cancer in stomach, œsophagus, pancreas, or duodenum; in a further 11 cases hæmorrhage was due to a blood dyscrasia, while in 4 even the pathologist was unable to detect a lesion at a complete examination. It is comforting to know that by far the most likely sites of bleeding are the stomach, lower œsophagus, or duodenum; but necropsy figures give a false picture of the incidence in clinical practice, since some conditions are less amenable to treatment than others—bleeding from œsophageal varices, for example—and thus more such cases come to necropsy. In a similar period (1945–54) 784 patients were admitted to the Toronto Western Hospital for treatment of upper-gastrointestinal hæmorrhage [4]; almost 80% of these cases were due to peptic ulcer and only 9% to œsophageal varices.

Why, then, is it difficult for the exploring hand and eye always to locate the lesion responsible for bleeding? Sometimes folds of mucosa hide an acute or superficial lesion with little induration to attract attention; sometimes a manifest lesion distracts attention from the site of bleeding, as when duodenal ulcer is associated with a bleeding ulcer in a hiatus hernia: Marchand [5] has reported bleeding in 37 of 138 cases of hiatus hernia, and in 19 this reached massive proportions. Surgery suffers from the limitation that the site of the lesion must be found if bleeding is assuredly to be stopped by excision or ligation. Wangensteen's [6] method of hypothermia using a refrigerating circulation within a balloon placed in the stomach—an apparatus similar to Khalil's [7]—has much to recommend it if further trials substantiate his original findings in 5 patients. The lesions included gastric and duodenal ulcer and œsophageal varices; in all 5, hæmorrhage ceased. Gastric hypothermia is therefore more widely effective in the anatomical sense than the surgeon, for it does not demand precise localisation of the lesion.

Langrall et al.[3] found no deaths due to hæmorrhage from the lower intestine and ascribe this to the fact that diverticulitis, ulcerative colitis, regional enteritis, polyps, and carcinoma (though they may cause bleeding) seldom cause exsanguination. Nevertheless they sometimes do, and Ulin et al.[8] describe 5 cases of "major" bleeding due to diverticulitis, in 1 of which emergency resection had to be undertaken because the patient seemed likely to die. The absence of bowel lesions from the Mayo Clinic necropsy series may reflect the relative efficacy of treatment. Nevertheless anyone who has been forced to open the abdomen on account of bleeding from the bowel will be aware that here, too, the exact site of bleeding, whether from diverticulitis or colonic telangiectasia,[9] is sometimes difficult to locate—though this difficulty can sometimes be overcome in blunderbuss fashion by the radical approach of transverse colostomy to locate large-bowel bleeding in the proximal or distal half, followed by the appropriate hemicolectomy.[10]

1. Quattlebaum, J. K. *Ann. Surg.* 1954, **139**, 743.
2. Sheldon, W. C., Lazar, H. P., Richards, J. W., Henegar, G. C. *Amer. J. dig. Dis.* 1959, **4**, 817.
3. Langrall, H. M., Baggenstoss, A. H., Wollaeger, E. E. *Proc. Mayo Clin.* 1960, **35**, 195.
4. Bingham, J. R. *Canad. med. Ass. J.* 1959, **80**, 704.
5. Marchand, P. *Brit. J. Surg.* 1960, **47**, 515.
6. Wangensteen, O. H., Root, H. D., Jenson, C. B., Imamoglu, K., Salmon, P. A. *Surgery*, 1958, **44**, 265.
7. Khalil, H. H. *Lancet*, 1958, i, 1092. Khalil, H. H., Mac Keith, R. *Brit. med. J.* 1954, ii, 734.
8. Ulin, A. W., Sokolic, I. H., Thompson, C. *Ann. intern. Med.* 1959, **50**, 1395.

ASCITES TUMOURS DESTROYED BY NON-PATHOGENIC FILTRATE

DURING serial grafting of an ascites tumour Bennette [11] found an unusual appearance in some of the grafted mice. This consisted in clumping of inoculated cells, absence of ascitic fluid, fibrinous exudates, and gelatinous degenerate tumour growths. These changes led to intestinal adhesions and death. Serial transplantation of the abnormal intraperitoneal tumours ended in their loss. From the same original source, however, the usual type of ascites-tumour cells had been maintained in other mice. All the host mice, which were of mixed stock, had been treated with vaccinia lymph as a prophylactic measure against ectromelia.[12] At this stage it became advisable to use line-bred mice as hosts for the grafts and C_3H were chosen. Bennette then found that, by adding vaccine lymph to Krebs-2 ascites samples before inoculation, or by injecting it intraperitoneally after implantation, the inoculated cells were destroyed, resulting in "no-takes". Addition of vaccine to tumour inocula induced the abnormalities that were seen originally. A less close association of abnormal growths with vaccinia, which has long been known to destroy certain mouse ascites tumours, was found in a subline which had shown no unusual features for many transfer generations. Typical ascites-tumour cells from this source were then grafted into C_3H mice which had not been vaccinated. In the tenth serial transfer in unvaccinated mice the characteristic abnormalities developed.

These and other observations led to testing of sterile filtrates of extracts of abnormal growths [13 14] for tumour-destroying capacity. Samples from one abnormal tumour subline which had been stored at $-50°C$ provided a bacterially sterile filtrate that had a potent destructive effect on five different kinds of ascites tumours.[14] A small group of normal mice which were given 10^6 times the tumour-destroying dose of filtrate were observed for two months without showing signs of illness.[14] The implication is that filtrates from degenerating ascites-tumour grafts can cause these same degenerative changes and even complete failure to "take" when injected with inocula of the usual typical ascites cells. As there was also evidence of increase with passage, the destructive factor is believed by Bennette to be a virus. Some attempts to demonstrate vaccinia itself have failed.[12] Control filtrates from typical forms of Krebs and Ehrlich ascites tumours prepared in the same way never gave rise to destruction of tumours or even modified the final yield, compared with untreated and saline controls.

The morphological degeneration in the affected ascites tumours is distinctive and is clearly unusual. Ascites growths have now been observed for over half a century, and if these changes were seen earlier they did not attract

9. Monroe, L., Steelquist, J. *Gastroenterology*, 1960, **38**, 650.
10. Sandegard, E. *Acta chir. scand.* 1959, **117**, 465.
11. Bennette, J. G. British Empire Cancer Campaign annual report, 1957; p. 19.
12. Bennette, J. G. *ibid.* 1958, p. 139.
13. Bennette, J. G. *ibid.* 1959, p. 13.
14. Bennette, J. G. *Nature, Lond.* 1960, **187**, 72.

much notice. Bennette's observations must clearly be systematically repeated before a firm conclusion is reached that an oncolytic ascites-tumour virus, which does the host no harm, has been found. If typical ascites-tumour cells can be obtained from a source uncontaminated by the agent in question, enough bulked agent can be stored for all series of tests, and adequate numbers of host mice of the same strain are inoculated alternately with tumour cells in the same experimental session either with or without the suspected agent as a filtrate, a decisive answer should be obtained.

MANAGEMENT OF THE INJURED

To many it seems that our accident service is less effective than it should be; and an authoritative committee is at present examining its deficiencies.[1] Reports published by the American Medical Association's Council on Drugs show that similar doubts beset the profession in the U.S.A.

Artz [2] writes:

"All physicians are extremely interested in the prominent older citizen who has prostatic difficulty, but few are interested in the rowdy youngster who is admitted, partially inebriated, in the middle of the night, with a gunshot wound or multiple injuries after an automobile accident. Most injured patients are admitted in the midst of a busy day or at night, and it has become common practice to shift the responsibility of the severely injured to younger physicians on the staff."

Brigadier-General Seeley,[3] after pointing out that after wars the basic principles of emergency treatment are often forgotten or overlooked, declares:

"The most experienced surgeon can contribute best in resuscitation, in appraisal of the wounded, and in determining priorities of care. His supervision of less qualified surgeons will effect greater care to greater numbers."

With regard to treatment itself, Altemeier and Wulsin [4] emphasise that the administration of various antibiotics is no substitute for early and adequate operation; and Wilson and Stirman [5] question the generally accepted view that blood-transfusion is a life-saver in the resuscitation of the badly burned patient: they claim much better survival figures for cases treated with simple electrolyte and fluid replacement, and they avoid infusing blood, plasma, dextran, and similar colloidal volume expanders. We may not all agree that there is "only one method" (exposure) of treating the burn itself—we are not all blessed with the climate of Texas—but the reminder of the dangers of the constrictive circumferential lesion is useful to those of us who are occasional burns surgeons. Reduction of lung "compliance" and loss of vital air capacity about the fourth or fifth day after burning will be new to some. Artz's emphasis on emergency first-aid treatment and on attention to "transportation" cannot be reiterated too often. But his view that a patient with multiple injuries should be treated by a general surgeon will not command unanimous agreement among orthopædists, who may feel that his assertion that "a fracture is about the only type of injury that will not kill the patient immediately" is not unanswerable. The articles include a timely one on "control of suffering in severe trauma".[6] How often in our own wards is this problem dismissed by the words "Give him a quarter"? There are other articles on resuscitation,[7] the early management of fractures,[8] and anti-tetanus immunisation.[9]

Not all that appears in these articles is applicable here: a solution that suits Pennsylvania may be none for Putney. Nevertheless, anyone thrown into a wall at sixty miles an hour will react to his injury in much the same way wherever that wall may be; and study of these careful and detailed reports will help to improve his chances of recovery. They may also highlight yet again the damage still done by accidents, which account for nearly 4% of all deaths.

THE MINISTER RESIGNS

On July 22 Mr. Derek Walker-Smith resigned the office of Minister of Health, which he had held since 1957, to go back to his practice at the Bar. His speech at the end of the Supply debate on July 21, which is reported on another page, was therefore in some measure an account of his stewardship. But by the terms of the debate it was inevitably a partial record. The figures he gave for new hospitals at different stages of building and planning remind us that a programme of capital expenditure is at last under way. This development, long overdue, will clearly influence the National Health Service for many years. Some of his remarks, by implication, also recalled events outside the hospital service which are likely to have a lasting effect. What he said about the growing number of outpatient clinics and day hospitals for mental patients reminds us of the shift from institutional to community care and the other major changes which are expected from the gradual introduction of the new Mental Health Act's provisions. His words on the revision of salary scales recall that acceptance of the Pilkington report has given the medical profession administrative machinery which, wisely used, should protect their independence and integrity. In preventive medicine the campaign for poliomyelitis vaccination has attracted public interest and won a large measure of public cooperation. As Mr. Walker-Smith readily admitted, much still remains to be done; but, as he put it, "we have struck our lines of advance and we are pursuing them vigorously and with a considerable degree of success".

His own task, as he saw it, has been ably fulfilled for three important years: and in regretting his return to his first love, the Law, we can at least look back with pleasure on his temporary liaison with Medicine.

Mr. A. C. H. Bell has been elected president of the Royal College of Obstetricians and Gynæcologists in succession to Sir Andrew Claye.

Prof. P. B. Medawar, who holds the Jodrell chair of zoology and comparative anatomy at University College London, has been appointed to succeed Sir Charles Harington as director of the National Institute of Medical Research when Sir Charles retires in August, 1962.

The oldest surviving member of *The Lancet*'s staff, Mr. J. A. Norris, died on July 20, which was his 90th birthday. Joining us in 1886, he worked in the advertising department, where his helpfulness and courtesy were widely appreciated. His quiet office life was surprisingly varied when he had the rare experience of being struck by lightning: but after his retirement in 1938 he remained in good health until two years ago. A man of scholarly tastes, with a liking for languages, he was long able to continue and to enjoy his visits to the British Museum reading-room.

1. See *Lancet*, 1960, i, 590.
2. Artz, C. P. *J. Amer. med. Ass.* 1960, **173**, 522.
3. Seeley, S. F. *ibid.* p. 518.
4. Altemeier, W. A., Wulsin, J. H. *ibid.* p. 527.
5. Wilson, B. J., Stirman, J. A *ibid.* p. 509.
6. Beecher, H. K. *ibid.* p. 534.
7. Howard, J. M. *ibid.* p. 516.
8. Hampton, O. P. *ibid.* p. 536.
9. Stafford, E. S. *ibid.* p. 539.

Public Health

VENEREAL DISEASE AMONG WOMEN PRISONERS

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A YEAR ago the Ministry of Health drew the attention of local health authorities to the recent rise in the incidence of gonorrhœa and to the part played by a relatively small group of promiscuous women in spreading this infection.[1] Since then their chief medical officer's report for 1958 has been published,[2] and the figures given in it suggest that the number of cases of gonorrhœa is still increasing and that in London and in some provincial cities prostitutes or "near prostitutes" are largely responsible for the spread of infection. The tracing, treatment, and follow-up of these girls is a serious social as well as a medical problem.

Many of them are unintelligent and uncooperative. Those infected often have no symptoms of disease and see no point in medical examination. Others with symptoms fail to take them seriously or avoid examination because they fear restriction of their activities. Those who do seek advice commonly fail to attend long enough. All these circumstances make it difficult to assess the incidence of infection among these women, though obviously it must be high.

A study of the medical records of women admitted to Holloway Prison during 1958 has provided a useful glimpse of the facts.

GENERAL POPULATION

Holloway Prison serves 23 counties, mainly in the south-east of England, but extending as far west as Dorset and as far north as the Wash. The prisoners are divided into those who are convicted and those who are on remand. Since 1950 most of the women in both groups have been examined and tested for venereal disease, though a few have refused examination, as they are entitled to do. With some the period of remand is short and only one series of tests is possible. In women with a chronic infection this may well be insufficient to establish its presence. Douching is common among prostitutes and often temporarily suppresses evidence of infection, which only becomes apparent days or weeks after admission to prison.

Of the 2706 women admitted during 1958, 2382 were examined and tested. 87 (3·2%) refused examination and 237 (8·7%) were discharged before an examination could be made.

Of the 2382 patients who were examined, 1921 (80·6%) had not been investigated or treated elsewhere. Of these 31 were found to have syphilis, 215 gonorrhœa, and 778 other conditions requiring treatment.

The stages of infection in the 31 cases of syphilis were as follows:

Primary	4
Secondary	4
Latent 1st year of infection	4
Cardiovascular	0
Neurosyphilis	7
Late latent	12
Congenital	0

Of the remaining 461 patients who were examined, 42 had been treated for venereal diseases at some other centre—7 for syphilis and 35 for gonorrhœa. 419 had been admitted to Holloway Prison during 1950–1957 and had already been investigated, when 44 had been found to have syphilis, 33 gonorrhœa, 127 other conditions needing treatment. In these women it was possible to assess the results of earlier treatment and to give further treatment when indicated.

Thus in the general population of the prison, of 1921 patients who were examined for the first time 31 (1·6%) were found to have undiagnosed syphilis and 215 (11%) undiagnosed gonorrhœa. These figures are certainly appreciably less than the true incidence.

155 of these women were pregnant; and of these 3 had syphilis, 14 gonorrhœa, and 96 other conditions needing treatment.

The Prostitutes

The number of known prostitutes admitted during 1958 was 464, compared with 292 in 1957 and 201 in 1956. Their ages, with the figures of 1957 and 1956 for comparison were:

Age (yr.)	*1958*	*1957*	*1956*
15–20	169 (*36%*)	83 (*28·4%*)	41 (*20·4%*)
21–25	132	73	56
26–30	52	46	32
31–40	68	57	50
41–50	33	22	15
51–60	10	10	7
61–70	0	1	0

There is an absolute and relative increase in the number of teenage (15–20) girls, and in 1958 they accounted for 36% of the total number of prostitutes admitted.

Of the 464 prostitutes 6 refused examination, 43 were not examined because their fines were paid and they were promptly released. Among the 415 who were examined 31 needed no treatment. Of the others, 23 had syphilis, 137 gonorrhœa, and 230 a vaginal discharge. 6 had both syphilis and gonorrhœa. Most of those with vaginal discharge needed further investigation, but this was not possible owing to the shortness of their stay in prison.

The stages of infection on the 23 with syphilis were as follows:

Primary	3
Secondary	4
Latent 1st year of infection	4
Late latent	8
Neurosyphilis	3
Cardiovascular *	1

Pregnancy was diagnosed in 2 prostitutes with syphilis, 9 with gonorrhœa, and 27 others.

Thus, 23 (5·5%) of 415 prostitutes who were examined were found to have syphilis and 137 (33%) gonorrhœa. Of the latter 17 were again found to have gonorrhœa when re-admitted during 1958, so the total number of gonorrhœal infections among these women was 154. Many others had evidence of infection but a firm diagnosis proved impossible.

The Teenager Prostitutes

Of the 169 teenagers 24 were not examined. Of the 145 examined, 4 (2·7%) were found to have syphilis, and 71 (48·9%) gonorrhœa. 8 were twice found to be infected with gonorrhœa during 1958.

DISCUSSION

The incidence of veneral disease, and particularly gonorrhœa, is thus high in the population of this women's prison. It is considerably higher among known prostitutes than among the prison population in general, and it is highest among the considerable and presumably increasing

1. *Minist. Hlth Circ.* 6/59. April 27, 1959.
2. *Rep. Med. Offr Minist. Hlth, Lond.* 1958; part II. H.M. Stationery Office, 1959.

* Not all the prostitutes were seen for the first time in 1958, which accounts for the presence of 1 case of cardiovascular syphilis not shown in the group of 31 cases.

number of teenage prostitutes. The number of cases of gonorrhœa found among teenagers accounts for more than 50% of the total number of cases in prostitutes. Most of these young people have little or no knowledge about venereal disease and seldom go of their own accord for investigation or treatment. Their ignorance is a serious source of danger to themselves and to their contacts and must lead to much spread of infection.

The system, which prevailed until the introduction of the Street Offences Act in August, 1959, whereby these women were, on conviction, sentenced to a fine of 40*s*. or 14 days in prison, hindered attempts to control infection. The fines of many were paid for them within twenty-four hours of admission, and this applied as much to the teenagers as to older women. This gave no opportunity for proper investigation and treatment. The regulation which proved most useful in this respect was section 26 of the Criminal Justice Act, 1948, which made it possible to send a woman to prison on remand for a physical and mental report if she was charged before a magistrate's court with an offence punishable by imprisonment. A girl admitted under this section was placed in the prison hospital and thoroughly examined, and venereologists, psychologists, medical officers and probation officers had an opportunity fully to investigate her health and circumstances with a view to treatment and rehabilitation.

During 1958, 162 prostitutes were admitted under section 26; 14 came in twice and 4 three times—a total of 184 admissions. Of these, 71 were found to have gonorrhœa; 10 had two infections during the year; 3 had primary syphilis; 2 early latent and 2 late latent syphilis; 1 had cardiovascular syphilis; and 1 had neurosyphilis.

It seems unlikely that the Street Offences Act will be as helpful as Section 26, and it may well prove a serious hindrance. The advantages to public order of clearing these girls from the streets are obvious, but the extension of the call-girl system is likely to strengthen the hands of pimps, ponces, and unscrupulous landlords and diminish the number of contacts with the law which in the past have been the only opportunity of dealing with this reservoir of infectious venereal diseases.

SUMMARY

Examination and testing of 1921 women admitted to Holloway Prison during 1958, who had not been investigated previously, showed that 1·6% had syphilis and 11% gonorrhœa.

464 known prostitutes were admitted during the same year, and of these 169 (36%) were in the 15–20 year age-group.

415 of these were examined and tested for venereal diseases, and 5·5% were found to have syphilis and 33% gonorrhœa.

145 of the 169 teenage prostitutes were examined. 2·7% of them had syphilis and 48·9% gonorrhœa. The number of cases of gonorrhœa found among them was 71, accounting for more than half of the cases among prostitutes.

Section 26 of the Criminal Justice Act of 1948 proved helpful in ensuring examination and treatment and rehabilitation of many of these women.

The Street Offences Act 1959 may hinder the detection and treatment of venereal infection among prostitutes.

My facts and figures are taken from the report of the venereological department of H.M. Prison, Holloway, for 1958 with the permission of the Prison Commissioners.

Gonorrhœa in Middlesex and in Cardiff

Middlesex

In his report for 1959 Dr. A. C. T. Perkins, medical officer of health for Middlesex, refers to a disquieting increase in the incidence of gonorrhœa. During the year new cases treated at venereal-disease clinics in the county totalled 845—178 more than in the previous year. "This almost certainly represents only a fraction of the true incidence since an unknown but probably considerable number of patients are treated privately by their own doctors. A disturbing feature of the position is the number of reports which are received from the clinics pointing to a rising proportion of teenagers and those in the early twenties in attendance."

Cardiff

IN a report to the health committee this month Dr. W. Powell Phillips, medical officer of health for Cardiff, gave some figures for new cases of gonorrhœa at two centres in the city. Whereas in England and Wales the incidence rose from 27,887 in 1958 to 31,334 in 1959 (an increase of 12·4%), in Cardiff the corresponding rise was from 289 to 423, or 46·4%.

The doctors who treated venereal disease, he said, emphasise that "it is not the prostitute who is today largely responsible for the spread of infection, but the young person who is quite promiscuous in sexual conduct". In 1959, of 63 females with gonorrhœa treated at one centre, 19 were teenagers: the corresponding figures in 1958 and 1957 were 4 out of 30 and 7 out of 19.

Discussing the action needed, Dr. Phillips pointed out that early treatment will prevent spread and recommended that the "special treatment clinic" should be in the outpatient department of the Royal Infirmary, and not in a separate section. "Lectures," he thought, "should be given to groups who are interested, but it must be stressed that this is a moral issue rather than a lack of knowledge." He proposes to hold a press conference to be attended by experts on venereal disease, those who have to treat its complications, and representatives of the Churches.

Medical Education

TESTS OF ANATOMICAL KNOWLEDGE

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IN 1956 Bull arrived at a conclusion that must have alarmed all teachers relying on the conventional written examination: an essay-type question in the final examination in medicine at Queen's University, Belfast, was apparently so inefficient in distinguishing between students that "a random allocation of marks would have been nearly as useful".

It would obviously be unwise to apply Bull's findings to all parts of the medical course. Anatomy, in particular, is a subject that includes a large element of factual knowledge and it may be assumed that a candidate imperfectly acquainted with the topography of the human body would not be passed by any examiner, whatever the method of testing. To check the validity of this assumption, a comparison was made between the results of an essay-type paper in anatomy and the evidence provided by other means of testing a candidate's abilities. The opportunity was taken also to evaluate the efficiency of the examiners.

A class of fifty students and three examiners took part in this experiment. The students were examined as follows:

(1) An essay-type paper at the end of the first year of anatomy.
(2) A multiple-choice paper during the same week.
(3) A series of seven 15-minute oral tests during their fifth term.
(4) The 2nd professional examination at the end of their fifth term.

In addition, one of the examiners (examiner A) made an assessment of the students' anatomical knowledge shortly before examinations 1 and 2, basing his estimate on the results of regular "sign-ups" of the different regions of the body and discussions with the students while demonstrating in the dissecting-room.

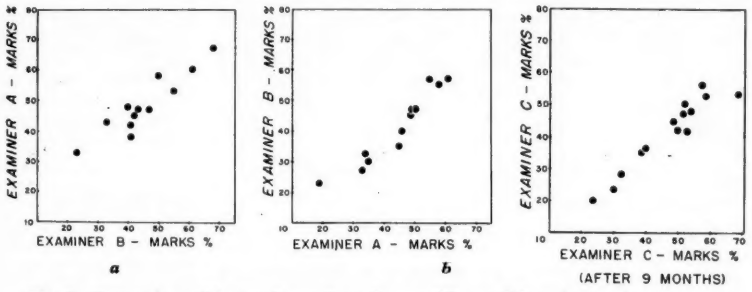

Fig. 2—Comparison of first and second marks scored by candidates (see text).

THE TESTS

The *essay-type paper* at the end of a year's work entailed the writing of five answers in three hours. A choice was given but the student was obliged to answer one question on neurology and one demanding some knowledge of embryology. The papers were marked by four experienced examiners (examiners A, B, and C and one other who took no further part in the present experiment). Some borderline candidates had their answers read again by a different examiner.

The results of the paper are shown in fig. 1a. Each candidate has been allotted a number coinciding with his placing in this annual examination and this number has been used throughout the remaining tests; candidate 16, for example, who scored highest marks in the multiple-choice test, was sixteenth in the essay-type paper. The first eighteen candidates scored over 50%, regarded officially as the pass mark. The black columns in fig. 1 denote subsequent failure in the second professional examination.

The papers were put aside for nine months, after erasing any marks from them that would have indicated the identities of the candidate and the examiner. Twelve of the papers marked by examiner A were then re-marked by examiner B, and vice versa. The results of plotting each candidate's original percentage against his subsequent one are shown in fig. 2a and 2b. On the whole the final placing was remarkably consistent, though examiner A was rather more lenient. Fourteen of the papers, formerly marked by examiner C, were handed to him again; he had dealt with many papers in the interim period and did not realise that he was marking the same batch for the second time. The result of plotting the first marks against the second is shown in fig. 2c. Again, the new percentages are very similar to the original ones.

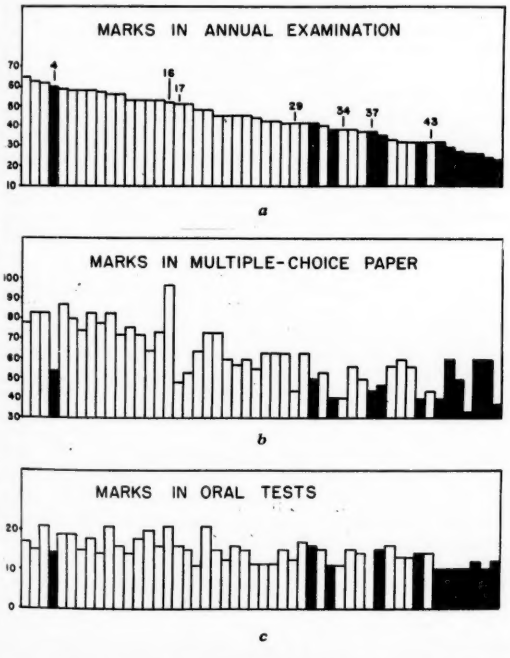

Fig. 1—Percentages obtained by fifty students in two examination papers (*a* and *b*) and the score out of a possible 21 in oral tests (*c*).

It appeared that there was surprisingly little examiner error in the marking of the essay-type paper, in contrast to Bull's findings. The question remains whether this type of test is in fact a good index of anatomical knowledge. That the answer is affirmative is suggested by the results of the other types of examination, set out below.

The *multiple-choice paper* resembled that advocated by Lennox, Anderson, and Moorhouse (1957). There were thirty questions, each offering a choice of five possible answers. The student was required to indicate which of the five he regarded as correct and was allowed ample time to complete the paper.

The results are shown in fig. 1b, the column representing any particular candidate being placed vertically below the corresponding column in the essay-type examination. A mark of 70% was arbitrarily chosen as the pass mark; 20 of these marks can of course be ascribed to chance for this could be the score of a candidate totally ignorant of anatomy.

Four candidates who passed the essay-type paper failed to score 70% in this multiple-choice test. Two who failed the paper exceeded 70%. In general, either test would have served equally well in distinguishing those possessing a good anatomical knowledge from those who lacked it.

The *oral tests* gave disappointing results.

They were conducted twice weekly by five examiners who gave a mark α, β, or γ for each viva-voce test lasting ten minutes. For purposes of comparison, these letters have been converted to 3, 2, and 1 marks respectively and the totals for all seven tests are shown in fig. 1c. Candidates 44 to 50 scored lowest marks but the results were not very helpful in sorting the candidates. These tests, each of which related to a circumscribed part of the body, would probably have been of more value if less restricted in scope. In addition, the standards and experience of the several examiners were by no means uniform.

The results of the *2nd professional examination* are indicated in fig. 1: a black column means that the candidate failed the examination, which consisted of two essay-type papers as well as practical and oral tests.

A detailed analysis of the marks is not possible but it can be seen that with one exception all who had passed the annual examination and/or the multiple-choice paper passed this examination also. A number who had failed both the annual examination and the multiple-choice paper passed, however; it is probably significant that only in the 2nd professional examination were borderline candidates permitted to benefit

from a consideration of class records. Moreover, there were undoubtedly some " late starters " among the 50 students.

Assessment of the candidates was in terms of *a* (knows enough), *b* (probably knows enough), *c* (probably below standard), and *d* (knowledge inadequate). The grouping was as follows:

Group *a*: 1, 2, 3, 5, 6, 8, 9, 10, 11, 13, 14, 15, 18, 19, 21, 22, 30, 34, 43.
Group *b*: 16, 17, 20, 24, 25, 26, 29, 32, 33, 35, 36, 39, 40, 49.
Group *c*: 4, 7, 12, 23, 27, 28, 31, 38, 41, 42, 47, 48.
Group *d*: 37, 44, 45, 46, 50.

Although the assessment was sometimes faulty (for example, candidates 7 and 12 obviously knew more anatomy than examiner A had realised) the grouping, made before any examination results were available, was in keeping with the evidence provided by the formal tests.

DISCUSSION

First, some comments may be made about the candidates specially indicated in fig. 1:

Candidate 4 did well in the annual examination but failed in other tests. He had evidently been fortunate in his " spotting " of questions in the written paper. Candidate 16 scored remarkably high marks in the multiple-choice paper. This man was later realised to be of outstanding ability and he was encouraged to take an honours B.SC. course in anatomy. Candidates 17, 29, and 34, by contrast, failed badly in the multiple-choice paper, a result not easy to understand. Candidate 37 was an unsatisfactory student who missed many of the oral tests (a score in which is therefore omitted from fig. 1); after failing the 2nd professional examination twice, he left the medical school. Candidate 43 was perhaps fortunate to pass the 2nd professional examination, in view of his past performance. However, it is noteworthy that he was assessed in group *a*; it may be that he was at first unable to exhibit his capabilities in the stress of an examination.

This study of examination methods and the consistency of examiners' marks has been reassuring. One cannot but feel that conventional methods have successfully sorted out those who knew their anatomy well from those who had an inadequate knowledge. There are no absolute tests of a student's familiarity with a subject, but in a small department in which the staff know the students the results of the 2nd professional examination yield few surprises.

SUMMARY

The anatomical knowledge of fifty students was judged by various examination techniques and by a personal assessment. The results were far more consistent than those recorded by Bull (1956) after investigating a final examination in medicine.

I wish to thank the examiners and students who made this study possible.

REFERENCES

Bull, G. M. (1956) *Lancet*, ii, 368.
Lennox, B., Anderson, J. R., Moorhouse, P. (1957) *ibid.* ii, 1957.

Special Articles

ORAL CONTRACEPTIVES

STATEMENT BY MEDICAL ADVISORY COUNCIL

THE Medical Advisory Council [1] of the Family Planning Association has given careful consideration to the question of the advisability of using the progestational steroid, norethynodrel, together with an œstrogen, as a contraceptive under the conditions planned for clinical trials in some of its clinics and is satisfied that it is perfectly safe for use in the way planned.

ADMINISTRATION

Patients who volunteer and who come within the age-range 25–35 years, and who have one or more children thus proving their fertility, will be given one tablet of norethynodrel 2·5 mg. containing ethinylœstradiol 3-methyl ether 0·1 mg. daily from the fifth day of the menstrual cycle for twenty days. The tablets will then be stopped and resumed again after an interval to allow for menstruation. Though a preliminary assessment will be made in six months, the trial will be continued for a year and patients will be followed up wherever possible for five years. The efficiency of this dose of norethynodrel has already been established in over 1000 cycles of administration. The object of the present trials is to work out improved methods of administration and to find the best possible practical instructions for patients.

Side-effects

Side-effects are known to occur in about a third of all patients who start taking norethynodrel. The incidence varies somewhat with the dose and with the dose of œstrogen. One of the objects of these trials is to determine the doses of norethynodrel and of œstrogen which will produce least side-effects. The majority of these are *gastrointestinal* symptoms—nausea, vomiting, headache—and are believed to be due to the œstrogen. They clear up spontaneously, however, after one to three cycles of administration and are relieved by antacids. *Break-through bleeding* occurs in about a third of the patients and can be bewildering to the patient and make the administration instructions more difficult. This, however, is quite harmless and settles down after three to four cycles. While previous investigators have increased the dosage to prevent break-through bleeding when it has threatened, we are advising patients to ignore spotting but to stop taking the pills if frank bleeding occurs and to start treatment again on the fifth day as if this had been a normal bleeding. There is no proof that *libido* is affected. In the majority of patients no change is observed; a few notice an increase, a few a decrease, in roughly equal numbers.

Some patients notice tenderness and tumescence of the *breasts* at the beginning, but this is reduced in later cycles and in some patients there is a noticeable reduction in breast fullness and size.

The majority of patients notice an *increase in weight* to begin with which settles down to normal after two to four cycles of administration.

RISK OF CARCINOGENESIS

The effect of the administration of progesterone and œstrogen, separately and together, have been considered. *Œstrogens* are known to cause abnormal changes in certain circumstances, particularly in the mammary glands. This is known in certain strains of mice which are prone to it anyway, but has not been shown in other experimental animals. Overgrowth of fibrous tissues are known which are definitely not malignant and are entirely suppressed by progesterones. There is no evidence of malignant growth. In any case, while continued stimulation may cause cancer in animals, interrupted administration is not usually considered to do so. In humans, though the incidence of cancer of the uterus is higher in women who have a high continuous level of endogenous œstrogen production, there is no evidence of administered œstrogens having this effect. No-one has shown that exogenous administration has ever produced cancer.

When *progestins* are administered alone there is no evidence that any changes in organs take place which can give rise to malignant growths. When œstrogen and progesterone are administered together, progesterone would seem to have a

1. The members of the Medical Advisory Council are: Sir Russell Brain (chairman), Sir Andrew Claye, Dr. J. A. Fraser Roberts, Mr. Ian Jackson, Prof. Norman Morris, Sir James Paterson Ross, Dr. G. I. M. Swyer, Sir Dugald Baird, Mr. Donald Fraser, Prof. Douglas Hubble, Sir Aubrey Lewis, Prof. W. C. W. Nixon, Mr. John Stallworthy, Dr. John Sutherland, and Dr. Eleanor Mears (medical secretary).

protective effect in humans as well as in guineapigs. The progesterone protects the animals from any adverse effects of œstrogen, and the balance of these pills is progestogenic instead of œstrogenic.

If these pills were administered to someone who already had cancer of the breast or uterus, it would appear that they would not cause harm and might have a tendency to arrest it.

LONG-TERM EFFECTS

The possible long-term effects of prolonged pituitary inhibition have been studied. In animals when pituitary activity is inhibited its effects are all entirely reversible with the exception that if the œstrogen is administered continuously to a rat for two-thirds of its life, pituitary adenoma may appear.

In women, œstrogens have been administered continually for medical reasons over at least eight continuous cycles and sometimes over years, yet when medication has been stopped ovulation has taken place in the next one or two cycles. Thus even constant administration of these steroids over prolonged periods of time does not appear to interfere with ovarian function on a permanent basis. Then too norethynodrel has been administered cyclically for contraceptive purposes to over 1000 women during 15,000 cycles of medication: the trials have in fact been going on for over five years altogether, and so far there does not appear to be any long-term effect on the ovary or pituitary.

Ovarian biopsies have been obtained from women who after using norethynodrel as a contraceptive for some time have wanted to be sterilised. These women were always sterilised during the last two weeks of a cycle and were medicated right up to the time of operation. None of these ovarian biopsies has ever shown a trace of corpus luteum. There has been no correlation between the numbers of primordial follicles and the duration of administration of the oral contraceptive.

Data available in the literature show that subsequent fertility is not affected whether after short or long courses of medication. As far as long-term effects on other endocrine glands is concerned, there appears to be no substantial effect on other glands except possibly on the adrenal cortex in which there is an average lowering of excretion of their products, which on intense study has been found to involve some alteration in the metabolism of hydrocortisone. There have been no symptoms of hydrocortisone deficiency in these women, and the blood concentration is well above normal level.

Recently, the United States Food and Drug Administration approved an application for the use of norethynodrel as an oral contraceptive, showing that they consider the information submitted indicates that norethynodrel is safe for use under the conditions which have been covered by the application—namely, the use of one 10 mg. tablet daily for twenty days each menstrual cycle, with the recommendation that such use be restricted to not more than 24 consecutive cycles for the time being. It will be seen that this dosage is four times the dosage being used for trials in this country.

Hirsuties

Some of the progestational steroids are androgenic, but this is not so with norethynodrel which is œstrogenic; there is therefore no danger of this with the preparation we are using.

Liver Damage

Some new synthetic steroids have been found to cause liver damage, but these have been androgens such as methyl testosterone. As a routine precaution, liver-function tests in representative groups of patients and also in controls have been carried out. Normal liver function is indicated by the results where norethynodrel has been the steroid administered.

Congresses

CONGENITAL MALFORMATIONS

THE First International Conference on Congenital Malformations was held in London on July 18–22 under the auspices of the National Foundation. The Foundation is an American organisation which, until recently, has been interested mostly in infantile paralysis, but is now planning to use some of its funds for research into congenital malformations. The purpose of the conference was to review all the different lines of approach, and the Foundation had gathered together many experts in different specialties who have studied the ætiology of malformations.

Prevalence

Prof. MAURICE LAMY (Paris) noted how estimates of the prevalence depended on whether stillbirths were included, the proportion of minor malformations that were included, and the length of time that the children were observed. Speaking generally, the prevalence of major malformations visible at, or seen after, birth, including stillbirths, was of the order of 1·5%. If one followed the children to the age of a year, and included some minor malformations, the figure went up to 4 or 5%. This was a formidable figure, and in technically advanced countries accounted for 15–20% of all infant deaths.

Prof. THOMAS MCKEOWN (Birmingham) noted some of the peculiar variations in the prevalence of individual malformations—for example, with maternal age and birth-order, with the season of the year, and with social class. Several malformations appeared to be commoner among firstborn children, and also to be more common with increasing maternal age. Two malformations—anencephaly and congenital dislocation of the hip—were more frequent in children born in winter. (Later Prof. JAMES WALKER reported that in recent years in Dundee the relationship was reversed.) Anencephaly was much commoner, at any rate in Scotland, in the lower social classes. Professor McKeown suggested that differences of this kind were, with reservations, likely to be due to variations in environment.

Intrinsic and Extrinsic Factors

Twenty years ago, said Dr. JOSEF WARKANY (Cincinnati) it was the study of environmental factors which led the field. Now the geneticists were making the running. But, as Dr. J. V. NEEL (Michigan) remarked, what is needed is a study of the part played by genetic and environmental factors in each specific malformation. Broadly speaking, less than 20% of malformations appeared to be simply determined by mutant genes, less than 10% by the newly discovered chromosome mutations, and less than 10% by virus infections, leaving more than 60% unaccounted for. Dr. Neel noted that, while the prevalence of individual malformations varied from country to to country, the total impact was much the same in widely different races—for example, Caucasians and Japanese. He suggested that there might be a regulated principle whereby malformed children were the price we paid for the advantages of being heterozygous at many gene loci, and he instanced the resistance to malaria possessed by the carrier of the gene for sickle-cell anæmia.

Prof. RAYMOND TURPIN (Paris) and Dr. W. M. COURT BROWN (Edinburgh) gave an account of the exciting new discoveries of chromosome abnormalities which are responsible for mongolism, Klinefelter's and Turner's syndrome, and " super-females ". These chromosome abnormalities were not uncommon; the prevalence of mongolism was close to 2 per 1000, and Dr. Court Brown observed that 1 " male " infant in about 400 had female nuclear sex.

Briefly reviewing the mass of experimental data on environmental teratogenic factors, particularly specific vitamin deficiencies, in animals, Dr. WARKANY declared that there was little or no evidence that any of these factors were important in man. Besides rubella, only cytomegalic inclusion disease, aminopterin and myeleran, certain endocrine preparations, and radiation had been incriminated in man; but our ignorance of environmental factors, he said, was not necessarily a measure of their importance.

The part played by virus infections was discussed by Dr. A. J. RHODES (Toronto). Apart from rubella, only influenza and mumps appeared to be possibly teratogenic. He noted, however, that attenuated viruses in domestic animals could be tetratogenic, and warned of the possible dangers of inoculating pregnant women with attenuated poliomyelitis viruses. Dr. F. L. HORSFALL (New York) suggested that we should pay attention to the numerous viruses which caused no clinical symptoms. Although they caused no symptoms after birth, they were not necessarily harmless to the embryo.

The interplay of intrinsic and extrinsic factors in the development and the origin of malformations was discussed by Dr. WALTER LANDAUER (Connecticut) and Prof. HANS NACHTSCHEIM (Berlin) with examples from their experimental studies on chickens, rabbits, rats, and mice. Crooked neck in fowl—not unlike the human Klippel-Feil syndrome—was due to a recessive gene which did not manifest itself in the heterozygote; but the heterozygote readily developed the malformation if a nicotinic-acid antagonist was injected into the egg. Professor Nachtscheim cited the example of a recessively determined cataract in rabbits, the development of which could be inhibited by dehydration of the animal in the sensitive early postnatal period.

Dr. RICHARD DOLL (London) discussed the findings relating the prevalence of malformations in districts of New York with the geological formations, and so to the presumed background radiation. A recent study in Scotland relating malformation-rate to measured background radiation did not confirm the implications of the New York study; Aberdeen, with the highest background, had the lowest malformation-rate.

General and Abnormal Developmental Mechanisms

Dr. EDGAR ZWILLING (Massachusetts) described the interaction of ectoderm and mesoderm in the developing limb bud of the chick. The ectodermal ridge at the tip controlled the development of the mesoderm proximal to it, but itself was dependent on this mesoderm for its integrity.

Dr. RITA LEVI-MONTALCINI (St. Louis) gave an account of inductive mechanisms controlling the development of the sympathetic nervous system in chick embryos. The growth of these nerve-cells was shown to be stimulated first by mouse-tumour transplants, and then by snake venom. Conversely, the sympathetic nervous system of the developing rabbit embryo could be selectively destroyed by a single injection of an antiserum prepared from snake venom.

Dr. C. L. MARKERT (Baltimore) described nucleocytoplasmic interactions of embryonic frog cells. If the nucleus of one of these cells was removed and placed in the cytoplasm of a nucleated cell of another species, the nucleus temporarily lost its power of stimulating cell growth when returned to its own cytoplasm.

Dr. CLARKE FRASER (Montreal) illustrated genetic environmental interaction by the different responses of two strains of mice to the teratogenic action of cortisone. He showed that the effect was to delay the closure of the palatal shelves, and this effect was greatest on the strain in which such closure normally occurred relatively late. He suggested that the teratogenic action of antimetabolites with their severe and specific effect was a useful tool in elucidating development mechanisms.

Dr. ETIENNE WOLFF (Nogent-sur-Marne) described how the hormones produced by the sex glands of the fœtus controlled its own sexual development. He and others warned the audience of the dangers of the use of androgenic steroids in the treatment of threatened abortion.

Other Topics

Dr. ANNE MCLAREN (Edinburgh) described the way in which the effect of the maternal environment on the developing embryo could be studied by the transplantation of the embryo, or even the fertilised egg, into a host mother.

Dr. D. G. MCKAY (Boston) described the evidence that many early human embryos were abnormal even before implantation; this abnormality, however, probably contributed to early abortion rather than congenital malformation.

Perspective

Prof. C. H. WADDINGTON (Edinburgh) reminded the audience of the embryo's powers of recuperation—powers that had been developed as a result of natural selection. The genetic basis of this resistance to stress had been studied in drosophila and found to be specific. There were no indications of any overall genetic resistance, which was perhaps unfortunate, as it meant that genetic gains could be for only one particular type of stability and so must come slowly.

Dr. E. L. TATUM (New York) discussed how it might be possible to overcome the biochemical weaknesses underlying genetic predisposition to malformation. The possible methods were: the replacement of a missing substance; the prevention of a toxic substance over-accumulating; the replacement of defective tissue by cell or tissue transplantation; and the replacement of one gene by another. In the far future there was the prospect of in-vitro synthesis of desoxyribose nucleic acid (D.N.A.), and of making better D.N.A. than that which occurred naturally. This was the ultimate in biological engineering.

Prof. L. S. PENROSE (London) discussed some of the more immediately practicable lines of study: the recognition of special genetic susceptibility to teratogens; the attempt to prevent by hormone treatment the increased risk of certain malformations with increasing maternal age, and the use of chemical selection against sperm cells with abnormal chromosomes.

Finally, Prof. ROBERT DEBRÉ (Paris) set out the kind of service needed to reduce the damage done by congenital malformations. There must be early diagnosis, expert surgery, psychological help to the family (congenital malformations, he said, were the last of the shameful disorders of man), and genetic counselling for the parents on the risks to further children.

Conclusion

The National Foundation may well feel satisfied by the success of this conference. Its aim was achieved, though many of the contributions consisted in reviews. The reviewing has now been done; and later conferences should, perhaps, be concerned more with new discoveries.

RECENT ADVANCES IN RENAL DISEASE

THE conference held at the Royal College of Physicians in London on July 22 and 23 was concerned with renal disease.

Structure and Function

Prof. D. A. K. BLACK discussed the ways in which understanding has increased about the function of the various parts of the nephron, with special reference to the loop of Henle and the counter currents which are thought to arise in it. Interest had centred in this part of the renal tubule since it was noted that only animals which had a loop of Henle were able to produce a concentrated urine. There had also been advances in knowledge of the ion-exchange function of the distal tubules.

Dr. O. M. WRONG discussed renal-function tests. The creatinine-clearance test was the most accurate practicable test of glomerular function, but it had technical difficulties, and the urea-clearance test was sufficiently reliable for ordinary clinical purposes provided the urine flow was greater than 2 ml. per minute. Greater accuracy was achieved by prolonging the test for three to five hours. Tubular function could best be studied by the ordinary urine concentration test. If vasoressin tannate in oil was given the night before the test the patient need not abstain from fluid, but could drink as he wished. In research laboratories the estimation of specific gravity with the hydrometer was being replaced by methods which measured the osmolarity of the urine by the depression of its freezing-point.

Dialysis

Acute renal failure and the use of the artificial kidney were discussed by Dr. M. D. MILNE and Dr. R. C. JACKSON. There were now 20 artificial kidneys throughout the country, and in

some regional centres as many as 75 patients a year were being treated. Dialysis had a special value in military as well as civil practice for patients with renal failure due to severe injuries, though it was less effective in this group than in patients with acute tubular necrosis due to medical and obstetric causes, and in acute nephritis. In the discussion it emerged that limiting factors which prevented its indefinite use included malnutrition due to prolonged protein starvation (which was obligatory in the treatment of anuria), and infection.

The Nephrotic Syndrome

Much has been learned about the varied causes of this condition, and Prof. J. R. SQUIRE described his studies on the plasma and urine proteins in this disease, using ultracentrifugalisation and immunoelectrophoresis. He said that specific protein patterns could be associated with specific structural changes in the glomerulus: but this was challenged in subsequent discussion because of the number of cases where the pathological changes in the glomerulus were mixed. Two major causes of the nephrotic syndrome were amyloidosis (sometimes associated with renal vein thrombosis and sytemic lupus erythematosus [S.L.E.]).

Discussing amyloidosis, Dr. LAVINIA LOUGHRIDGE concluded that the only effective treatment was prevention by the better management of the diseases which caused it.

Important new work on S.L.E. was described by Dr. P. FREEDMAN who had studied antigen-antibody reactions in the cells of the kidney. In frozen sections from biopsy material he demonstrated a destructive action on the nuclei of the glomerular cells by antibodies from the patient's own serum made visible by tagging them with fluorescent dyes—an ingenious marriage of the techniques of clinical medicine, conventional histology, serology, and histochemistry. These circulating antibodies had been found only in S.L.E. and not in acute nephritis where they might have been expected. They were present in the γ-globulin fraction of the serum and their action depend on the presence of complement.

Prof. G. A. SMART and Dr. W. W. HOLLAND described the treatment of the nephrotic syndrome. The prognosis had improved greatly in the past ten years, but Lord EVANS suggested that this might be due to a change in the natural history of the disease rather than to steroid therapy, apparently so successful. Discussion revealed a clear need for a cooperative controlled study to decide this point, and also to show whether steroids were most effective if used continuously or intermittently. In addition to steroids, high-protein diets, diuretics, and measures to control intercurrent infections had an important place in treatment.

Pyelonephritis

Pyelonephritis is the commonest lesion of the kidney found post mortem, and is due to direct infection of the kidney parenchyma with microorganisms. The method by which these organisms reached the kidney, whether by ascending or by blood-borne infection was discussed by Prof. M. L. ROSENHEIM. There was evidence from renal biopsy that even a single mild attack of pyelitis might be associated with infection of the renal tissue, and there was evident need for better methods of detecting subclinical urinary infection, especially in children and pregnant women. Prof. H. E. DE WARDENER pointed out that the line of advance here might be by quantitative bacteriological studies, or by white-cell excretion-rates after provocative pyrogen injections.

The function of the urinary system itself might predispose to pyelonephritis, and Dr. D. EDWARDS described his radiological studies of the micturating cystogram. When the bladder was filled through a catheter with radio-opaque material, its behaviour during the act of micturition could be studied by fluoroscopy and recorded on still or cine film, and in some patients it had been found that urine was forced back up the ureters during micturition. This phenomenon of vesico-ureteral reflux had been noted commonly in patients with pyelonephritis, including small children. Other radiological signs of chronic pyelonephritis detectable on intravenous pyelography, described by Dr. C. J. HODSON, included dilatation and deformity of the renal calices, asymmetrical involvement of the two kidneys, and a loss of renal substance with contraction of their outline.

Medicine and the Law

The Black Box

IN 1956 the plaintiff bought for £110 a 'De la Warr Diagnostic Instrument' (referred to throughout the hearing as the "box") from the defendant, its inventor and manufacturer. The plaintiff now claimed damages for fraud, alleging that she had relied on the defendant's representations that the box was capable of identifying radiations said to be associated with all matter and could enable the operator to diagnose diseases and conditions of the mind and body.

Among the witnesses called for the plaintiff were Sir Robert Macintosh and Dr. H. G. Epstein, who said that they had visited the De la Warr laboratories at the request of a benefactor who was prepared to donate a substantial sum of money if satisfactory results could be obtained from agreed tests; that when Sir Robert suggested giving the defendant blood specimens of both diseased and healthy children, the defendant said that he might diagnose disease in the healthy children because they might contract the disease later, and when the blood of patients known to be about to die was then offered he refused that test; a preliminary test in which the defendant was to diagnose tuberculosis in guineapigs had failed.

Two other witnesses said that they had investigated the "radionic camera," a device said to be capable of taking "photographs" of things or persons not present at the time; in the course of one test an image had appeared after development on a plate which had never been put in the camera. An electrical engineer said that the box bore no relation to any scientific instrument.

The medical witnesses for the defence included Mr. Kenneth Walker, who said that he thought radionics was in line with modern ideas that everything had lines of force and put out radiations. Dr. T. T. B. Watson said that he thought the box enabled the operator to make contact with his unconscious mind, which could then be used like an electronic computor. Dr. Philip Langton-Lockton said that no-one could say how the box worked, but he had every confidence in the defendant; all disease was psychologically engendered, and was the outcome of subconscious conflict and psychological tension; it was somewhere on this level that radionics must work; the radionic camera did not take a picture of anything physical, but of the question you had asked. Dr. G. I. Evans said that the box was an application of Einstein's unified field theory and Eddington's fundamental theory. Dr. Mary Stevenson said that she had successfully used a box for diagnosis for ten years. A number of non-medical practitioners produced case-histories.

Mr. Justice DAVIES said that radionics was anything but exact science; there was, however, a great body of opinion holding a belief in radionics, and this could not possibly be ignored. Despite the criticism to which the defendant himself was open, his Lordship had been impressed by the way he and his family and his witnesses had given their evidence. He found that the defendant honestly believed the box worked and the plaintiff had the latent ability to operate it. That finding was decisive of this case. His Lordship was not deciding that the box did work; that was a very open question. The totality of the evidence suggested that the camera was completely bogus, but again his Lordship found that the defendant believed in the camera no less than in the box. Judgment for the defendant.

Philips *v.* De la Warr—*Queen's Bench Division:* Davies, *J.*, July 18, 1960. David Karmel, Q.C., and D. R. Stuckey (Woolley, Tyler & Bury); Christmas Humphreys, Q.C., R. J. Trott and Miss R. Denfield (M. A. Jacobs & Sons).

M. R. BARRINGTON
Barrister-at-law.

In England Now

A Running Commentary by Peripatetic Correspondents

It's not every day a lorry goes through the road outside our hospital. First thing I saw were two rows of red lanterns with notices "Road Closed". A student lark, I thought, obviously perpetrated by the lads from St. Ethelred's nearby (and done before too), but the equipment had a solid borough council look and a patrolling constable lent weight to the affair. My family was agog for the inside story, having heard on the 6 o'clock news that the road had fallen in and that a bomb was suspected to lie beneath. Others shared their interest and our hospital then flashed briefly into the public gaze. The Army was alerted, and the chief of our kids' department recalled in an evening paper the night in the blitz which he and another now eminent consultant spent on the roof of the hospital while the bombs fell all around. The administration sprang into action with thousands of cyclostyled notices on Plans for Evacuation.

Rumours abounded. One story was that the road just fell in, but it really was a friend of ours who helped resuscitate the driver whose suddenly disappearing wheels reactivated whole vistas of primal fears. Bomb experts were not at all interested in our hole (to the relief of the administration). Some then wondered if the patients were to blame having been lately shown the slightly ill-chosen *Wooden Horse* film. But in the end it turned out to be only a broken sewer, so we have all sunk back into our normal obscurity, and only a patch of new tarmac marks the spot where, as one of our wits put it, "the concrete became abstract".

* * *

If you join Burns in his lament, "Oh wad some Pow'r the giftie gie us, To see oursels as others see us!" I advise a night at the Ciba Foundation, kindly hosts to foreign visitors and to the odd native if a room is free. Breakfast is at 8.30 and when I arrived at 8.35, an American with his wife, a New Zealander, and an Italian were present. What a friendly feeling is imparted as they rise and introduce themselves by name and we shake hands. Two Germans and three Frenchmen join us. Soon the conversation turns to taxi-drivers who keep to the left and upset their conditioned reflexes and to the advantage of having a left hand drive so that the foreigner can put his head out of the window to converse with others as they wait at the traffic lights. But the big joke is the Englishman in the city on the hottest day of the year with his dark suit of thick material, complete with waistcoat (laughter), and bowler hat (more laughter), and not forgetting, as the Frenchman added, his umbrella (still louder laughter).

* * *

The other day I took my fountain pen to hospital. I hadn't an appointment but the receptionist was sympathetic and said I could wait. I took a seat on a bench in the waiting-room alongside several other casualties. At the far end of the room, behind a long desk, uniformed clerks recorded pen-owners' complaints and undertook diagnostic examinations. Pens in need of specialised attention were whisked out of sight to an upstairs laboratory by vacuum cassettes. After a period of careful observation, I decided that outpatient therapy was not greatly favoured and that most pens were recommended admission for periods of up to a week. An ill-concealed despondency in prognosis was exemplified by a brisk trade at the new pens' counter.

When my turn came, I was agreeably surprised by the hygienic condition of the top of the desk considering the nature of most of the complaints, achieved no doubt by virtue of an unstinted stack of blotting-paper. (Pædiatricians take note.) My clerk, an attractive girl in her early twenties, reminded me of a certain medical school, for her pen-side manner was coldly efficient and strictly impersonal. A few pointed leading questions rapidly brought my rambling history to a close. The rest of the consultation was equally disconcerting. Wilful neglect on my part over the course of the years was the chief cause of my pen's breakdown, and the young lady did not mince her words.

"You've dropped it," she accused me, having examined the nib at length with a magnifying glass. I protested my innocence but she obviously thought I was lying. "How do you account for the fractured cover?" she demanded. "You need a new barrel." In the interests of economy I resisted. "It affects your ink flow," she warned, but I maintained the obstinate asininity of the layman, though luckily she did not make me sign a refusal-of-treatment form.

Next she squeezed all the ink out on to some blotting-paper and examined it like a specimen of urine. "Do you make a habit of mixing your inks?" she asked scathingly. "No wonder your bladder is clogged." (How is one to explain that sometimes and in all walks of life one may have to avail oneself of whatever facilities are conveniently at hand—e.g., dipping a gold nib into a National Health Service ink-pot.) "It must go upstairs for a new bladder," she prescribed finally. "Will you leave it or wait?"

Obviously I waited, or I should not have been able to write this down.

* * *

I suppose those of my colleagues who do obstetrics are used to it, but I was a little doubtful of accepting at first. Still, I reasoned, he was a handsome creature, sleekly clothed in blue and white with splendid white moustaches. His voice was melodious though perhaps a little loud, and he seemed lively and intelligent. I agreed therefore to let my patient name her budgerigar after me.

* * *

We would recommend that no psychiatrist who has not himself been a child should attempt to become a child psychiatrist. Without this preliminary experience the job is virtually impossible. How else, for example, is one to know the rules of snakes and ladders? What other upbringing teaches one how to make paper gliders, both jet and conventional, and paper boats? Most important, how otherwise does one learn the technique of battleships? Books have been written on the comparatively simple games of chess, canasta, and bridge, but this fascinating game still awaits a worthy chronicler.

We must confess however that childhood is not in itself adequate training for the aspiring child psychiatrist; we have had to draw on our maturer knowledge of men and affairs in order to be able to lose at noughts and crosses without actually cheating.

* * * *

The trout and salmon fishing season has begun. I view it with mixed feelings, for while I am enjoying an evening fishing in the river which runs in the valley below the house, I am as often as not called back to the surgery to remove a hook from some overenthusiastic small boy. Saturday evening was such an occasion. The small boy's father, all talkative 250 lb. of him, was anxious to assist at the operation, and together we removed a very battered Dark Montreal. As I was working, it occurred to me that last summer I had spent an afternoon sewing up this small boy's eldest brother after a chance meeting with a chain-saw. In the autumn, the middle brother was brought in from a duck-hunting expedition, having managed to blow away best part of his foot. I said to Dad that the family was rather unfortunate. "Ah yes," he sighed. "We was always like that: me Dad was blowed to pieces when the breech of a six-inch gun exploded."

Yesterday afternoon, as I walked down the main street of the village, he shouted out to me, "Hi, Doc, me young feller's all right. How's about you and me taking a gun and going out sealing?" The hair on the back of my neck prickled and very tactfully I declined the offer. After all, he is as yet the only unscathed member of that family.

* * *

"I'm afraid they will have to come out," the family doctor said after examining the child's tonsils. Mother accepted this stoically; but as the doctor walked away down the garden path the child ran up to him and asked: "Please, must they come out? Couldn't they just be filled?"

Letters to the Editor

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—Everyone is extremely pleased at the progress made in the treatment of mental disease over the past few years and the resultant concern shown by the general public in the condition of our mental hospitals, together with the better integration of psychiatry and general medicine.

There is unfortunately a less happy other side to this coin which has received inadequate professional and public attention and which is causing a good deal of anxiety not least to general practitioners and to relatives of those suffering from a mental illness. All hated the prison-like neglected atmosphere of some older mental hospitals with so great an emphasis on lock-and-key and little else, but the efforts of many psychiatrists to pursue an excessively open-door policy with regard to mental treatment supervision seems to be gaining an unwise momentum and developing into a fashion with the impermanence and superficiality that the word fashion implies. The emphasis now, with a tendency to disregard other considerations, is quick turnover of patients, low bed-occupancy rate, outpatient treatment, day hospitals, hostels, extra social workers, sheltered workshops, anything in fact to keep a mentally ill patient from being in an asylum, and I use the word meanfully, and, if he is admitted, to discharge him just as soon as is humanly possible.

Dr. Denis Leigh [1] writes of schizophrenia in general practice and is evidently in sympathy with the trends I have described, but his writing is also of particular interest in demonstrating the apparently ambivalent attitude of modern psychiatry which on the one hand supports the fashion and on the other describes, as it knows so well, the terrible misery that psychiatric illness can cause when the sufferer is not in a mental hospital. Many general practitioners and others who know mental illness in the community may well feel that Dr. Leigh puts too much faith in the powers, opportunities, and efficiency of social workers, health visitors, psychiatric social workers, and others, in dealing with the awful problems that arise. In my experience these ancillary helps can do little more than try to get the patient accommodated, help with financial problems (of course, only in an advisory capacity), and generally to display sympathy. As soon as any serious problem arises directly from mental disturbance there is little they can do and, as the *Times* pointed out in a leader recently, there is no sign that local authorities have anything like enough staff, training facilities, or other provisions which the Government expects.

Dr. Leigh describes several of the problems that may arise. Firstly, quoting Carstairs, "17% of the patients (schizophrenics) were rated as causing serious social liability defined as the expression of violence, sexual deviation, callousness, paranoidal accusations and suicidal threats". He continues his own opinion: "the most disturbing manifestations are violence and sexual deviation, leading, as they may, to police action, and all that that can imply to a respectable family. The schizophrenic's sudden impulsive outburst of aggression is proverbial, and is often quite unpredictable . . . matricide is almost always a schizophrenic crime . . . venereal disease, pregnancy, and police action may again bring misery to the unfortunate family".

He states later that schizophrenics may wish to marry—like with like—"children of such matings have a 68% chance of developing schizophrenia. In view of the inaccessibility to reason shown by many schizophrenics, it is difficult, if not wellnigh impossible, to influence a decision made by two schizophrenics", &c. A difficult problem to say the least for any social worker or for anyone concerned with the welfare of children.

These quotations indicate just a few of the social miseries Dr. Leigh expects the community to have to face in the near future and it is small wonder that some feel that the anti-mental-hospital pendulum has swung too far in one direction. The general grey unhappiness that might exist in a mental hospital is no worse than the islands of private black misery which will exist in many households.

This is a distortion of progress and with Mental Health Year to remind us of the need it seems a great pity if the Government is given on a platter an excuse to avoid once again spending money on mental hospitals and repairing the ravages of past Government neglect. This is too convenient for an evasive Government, and an emphasis must remain on the need for humane modern mental hospitals.

I do not intend to be an advocate of a reactionary attitude towards mental illness: the present development of the social conscience towards this terrible suffering is wonderful to see. However, it would be a great pity if modern changes were spoilt by over-enthusiasm backed by a Government glad to have an excuse to avoid its responsibilities, and leading us to a future, after some years of social misery, when mental hospitals will have to be reinvented.

London, W.13. R. E. W. OLIVER.

1. Leigh, D. *Practitioner*, 1960, **184**, 702.

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—In an article you published on Feb. 6 we recorded six months' experience with bretylium tosylate, and drew attention to the poor results with patients who had retinal hæmorrhages, exudates, or papillœdema. The results with patients whose hypertension was not in the accelerated phase seemed at that time reasonably satisfactory. We have now followed the progress of these patients for between eight and eighteen months. The long-term results in all groups now seem so bad that we feel they should be recorded. We have done this in the accompanying table.

Only 9 of the 54 patients are still being treated with bretylium and of these only 5 have a blood-pressure on standing of 160/100 mm. Hg or lower on most occasions. Our results are getting progressively worse. In the first six months most patients with malignant hypertension or retinitis became resistant to the drug; over succeeding months the great majority of the less severe cases have also become resistant. The clinical condition of a few patients has deteriorated calamitously

LONG-TERM RESULTS OF TREATMENT WITH ORAL BRETYLIUM

Indication for treatment	No. of patients	Reason for failure of treatment			Still on treatment	Indication ended
		Death	Drug resistance	Intolerance*		
Malignant hypertension (papillœdema)	12	5	3	3	1	
Grade-3 retinal changes (hæmorrhages and exudates)	12	1	6	2	3	
Severe hypertension with symptoms	18	1	12	1	4	
Asymptomatic hypertension complicating chronic nephritis	9		6	2	1	
Hypertension in pregnancy	3		1	1		1

* includes side-effects and irregularities of hypotensive action.

between visits to the hypertension clinic because of developing resistance to bretylium.

Because of the high incidence of drug resistance and the irregularity of action of bretylium we do not intend to treat any more patients with this drug.

Department of Medicine,
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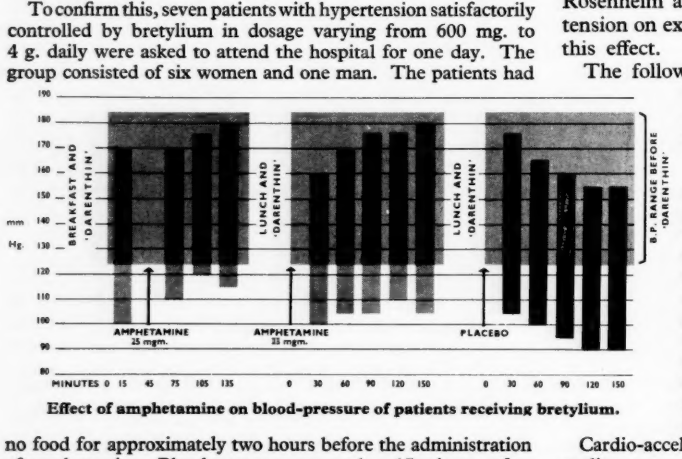
London, W.12.

C. T. DOLLERY
D. EMSLIE-SMITH
J. MCMICHAEL.

ACTION OF BRETYLIUM ANTAGONISED BY AMPHETAMINE

SIR,—During a current clinical trial of bretylium tosylate ('Darenthin') it was observed that four patients on amphetamine compounds to reduce their weight failed to show any response to bretylium. On withdrawal of amphetamine a satisfactory fall in blood-pressure was recorded and maintained on 1–2 g. daily. It seems therefore that the hypotensive action of bretylium is opposed by amphetamine.

To confirm this, seven patients with hypertension satisfactorily controlled by bretylium in dosage varying from 600 mg. to 4 g. daily were asked to attend the hospital for one day. The group consisted of six women and one man. The patients had


mm Hg.
BREAKFAST AND 'DARENTHIN'
LUNCH AND 'DARENTHIN'
LUNCH AND 'DARENTHIN'
B.P. RANGE BEFORE 'DARENTHIN'
AMPHETAMINE 25 mgm.
AMPHETAMINE 25 mgm.
PLACEBO
MINUTES 0 15 45 75 105 135 0 30 60 90 120 150 0 30 60 90 120 150

Effect of amphetamine on blood-pressure of patients receiving bretylium.

no food for approximately two hours before the administration of amphetamine. Blood-pressures were taken 15 minutes after arrival at hospital. 30 minutes later each patient was given 25 mg. of amphetamine orally. After this, blood-pressure recordings were made in each case at 30-minute intervals for $1^1/_2$ hours. A definite rise was recorded in six cases. One patient (male) who forgot to take his morning dose of bretylium before coming to hospital and who was given it 30 minutes after arrival showed a preliminary drop in blood-pressure followed by a sustained rise (see table).

After an interval of $1^1/_2$ hours (for luncheon) blood-pressures were again taken, and five patients were given 25 mg. amphetamine and two patients a placebo. Again blood-pressures were taken in all patients at $^1/_2$-hour intervals for $2^1/_2$ hours. The blood-pressure of those given amphetamine showed a sustained rise during the afternoon. There was a gradual fall in the two people given a placebo. The entire group took their accustomed dose of bretylium during the day.

It is common practice to try to reduce the weight of patients with hypertension, and it is therefore an important practical point that treatment with amphetamine antagonises the action of bretylium. The fact that amphetamine antagonises bretylium provides a potential research lead to the mode of action of bretylium and the pathogenesis of hypertension.

Royal City of Dublin Hospital,
Dublin.

ROBERT WILSON
CARMEL LONG.

SYNCOPE ON EXERTION DURING TREATMENT WITH BRETYLIUM TOSYLATE

SIR,—Dr. Turner and Dr. Lowther (April 2) emphasised that patients with hypertension controlled with bretylium may have syncope on exertion. Professor Rosenheim and Dr. Lowe (March 19) also noted hypotension on exertion but could not suggest a mechanism for this effect.

The following observations suggest a mechanism for the exertional hypotension and syncope which have been seen during treatment with bretylium.

Direct stimulation of the sympathetic nerves to the heart produces increased systolic pressure, greater ejection, and tachycardia.[1] A sympathetic vasodilator outflow from the hypothalamus, through the medullary and sympathetic nerves, to the blood-vessels in skeletal muscle has been demonstrated.[2–6] Rushmer and Smith [7] suggested that a mechanism may exist by which vasodilation in skeletal muscle and appropriate changes in cardiac function can originate from higher levels of the central nervous system in anticipation of exertion or abruptly at the onset of exertion.

Cardio-acceleration produced by stimulation of the inferior cardiac nerve was blocked by bretylium, but also the usual effect was reversed, since cardiac slowing was produced on stimulation. This effect was abolished by atropine.[8] Bretylium also reduced the reflex hypertension caused by stimulating the central end of the cut vagus nerve and the hypertension caused by carotid occlusion in the cat.[8]

1. Anzola, J., Rushmer, R. F. *Circulation Res.* 1956, **4**, 302.
2. Eliasson, S., Lindgren, P., Uvnäs, B. *Acta physiol. scand.* 1952, **27**, 18.
3. Erici, I., Folkow, B., Uvnäs, B. *ibid.* 1952, **25**, 1.
4. Eliasson, S., Lindgren, P., Uvnäs, B. *ibid.* 1953, **31**, 290.
5. Uvnäs, B. *Physiol. Rev.* 1954, **34**, 608.
6. Folkow, B. *ibid.* 1955, **35**, 629.
7. Rushmer, R. F., Smith, O. A., Jr. *ibid.* 1959, **39**, 41.
8. Boura, A. L. A., Green, A. F. *Brit. J. Pharmacol.* 1959, **14**, 536.

BLOOD-PRESSURE CHANGES IN 7 PATIENTS GIVEN BRETYLIUM AND AMPHETAMINE

—	Patient no. 1*		Patient no. 2		Patient no. 3		Patient no. 4		Patient no. 5		Patient no. 6*		Patient no. 7**	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D
Before bretylium therapy ..	160	130	160	120	170	120	260	150	200	125	205	105	200	125
During bretylium therapy ..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
15 min. after arrival at hospital ..	200	90	160	90	150	95	200	110	200	110	150	90	200	120
							Amphetamine 25 mg.							
30 min. later	170	105	150	95	140	110	200	130	230	110	145	95	200	105
60 min. later	180	120	180	105	160	120	230	145	180	120	170	120	200	125
90 min. later	200	125	170	105	170	105	200	120	200	105	190	120	200	125
							90 min. interval for lunch and bretylium							
After lunch	200	125	150	95	160	95	200	105	170	100	170	105	180	105
							Amphetamine 25 mg.							
30 min. later	180	120	145	100	180	120	200	125	180	110	170	100	200	115
60 min. later	180	115	150	105	160	115	225	130	180	115	160	95	200	110
90 min. later	170	105	170	105	160	110	210	130	175	120	160	95	210	130
120 min. later	170	95	170	105	140	105	210	130	210	115	160	90	210	120
150 min. later	170	90	170	95	150	100	210	125	210	115	160	90	190	105

* Patients nos. 1 and 6 were given a placebo instead of amphetamine during the afternoon session.
** Patient no. 7 omitted to take his morning dose of bretylium.
S = systolic. D = diastolic.

Syncope on exertion could be explained in the following way. With exertion there is increased sympathetic activity. Normally this would result in increased heart-rate and a rise in blood-pressure. However, in a patient who has been given bretylium there is a sympathetic adrenergic blockade. Thus there is no increase in heart-rate, but instead, cardiac slowing, presumably due to an unmasking of cholinergic sympathetic activity, since this effect was abolished by atropine in the cat. Further, the compensatory rise in blood-pressure will be not only blocked but also reversed, since bretylium blocks the effects of sympathetic adrenergic vasoconstrictor fibres but not sympathetic cholinergic vasodilator fibres.

If it is correct that syncope on exertion in patients on bretylium is due to cholinergic sympathetic activity, this side-effect should be abolished by atropine. Combined bretylium-atropine therapy would have little, if any, advantage to offer over the ganglion-blocking drugs, since parasympathetic blockade would also be produced. In fact, the only final difference would be on the adrenal medulla; ganglion-blocking drugs abolish the effect of nerve stimulation on the adrenal medulla while atropine and bretylium do not.

Department of Pharmacology,
University of Sydney,
Sydney, Australia. K. BRANDON.

PAROTID PAIN DURING TREATMENT WITH BRETYLIUM

SIR,—Pain in the parotid region, especially during meals, is a side-effect sometimes noticed when bretylium is used in the treatment of hypertension.[1–3] Some observations on the effects of this drug on salivary glands, made in anæsthetised cats, may help to explain the mechanism of this phenomenon.

The submaxillary or parotid ducts were cannulated; and the carotid blood-pressure and the blood-flow through the submaxillary gland were recorded. Bretylium tosylate ('Darenthin') was given intravenously.

Salivary secretion induced by sympathetic stimulation was diminished by doses of 0·3–0·5 mg. per kg. and abolished by 0·5–1 mg. per kg. bretylium tosylate. In order to reduce or abolish the vasoconstriction in the gland caused by sympathetic stimulation, 0·5–2 mg. per kg. was required. The secretory effect of adrenaline was not abolished even by large doses of bretylium, neither were secretion and vasodilation produced by stimulation of the chorda tympani.

Clearly this effect of bretylium in salivary glands corresponds to the "adrenergic neurone-blocking action" of the drug observed on the nictitating membrane and many other structures by the early investigators in this field.[4–6] The salivary glands seem particularly susceptible to this action.

Bretylium exerts in addition a muscarine action on the salivary glands. A dose of 1–2 mg. per kg. causes a flow of saliva, obtainable after the acute or chronic section of the chorda or removal of the superior cervical ganglion. After the chronic operations the secretory effect is even augmented. In the parotid gland bretylium still causes salivation after degenerative section of the postganglionic parasympathetic nerve. The secretory effect remains after hexamethonium or dihydroergotamine but is abolished by atropine. A vasodilation is, likewise, easily evoked by bretylium even in the decentralised gland; this response is also abolished by atropine. Some muscarine effects of bretylium have been described [6]; in the gland they seem to be evoked by remarkably small doses.

Parotid pain during meals has been observed by Gardner and Abdullah following extirpation of the superior cervical ganglion.[7] The pain was attributed to excessive hyperæmia in the salivary gland deprived of the normal vasoconstrictor action of the sympathetic neurones. A similar mechanism could be responsible for the pain described during treatment with bretylium. One action of this drug, easily elicited in salivary glands, imitates sympathectomy. The muscarine action of the drug on the gland may further contribute to an exaggerated hyperæmia in connection with a meal.

We are very grateful to Dr. A. F. Green, of the Wellcome Research Laboratories, for a gift of this drug.

Institute of Physiology,
University of Lund,
Sweden. N. EMMELIN
J. ENGSTRÖM.

TOO MANY CALORIES

SIR,—Your leading article of June 11 is at pains to point out the transient nature of changes in rates of body-weight loss which occur when calorie-deficient diets of fat and carbohydrate are fed alternately to obese patients. During my observations [1] on 24-hour respiratory quotients (R.Q.s) in obese subjects fed on dextrose it appeared that up to 10% of inspired oxygen could have been used for the net desaturation of lipid, leaving the fat molecule intact.

If we take the hypothetical case of an obese subject with 50 kg. of depot fat existing as tristearin, the consumption of 50 g. of oxygen per day for combination with hydrogen to form triolein and water could continue for a period of approximately 50 days. This is apparent from the chemical formulæ of tristearin and triolein, though the length of time during which desaturation could proceed would be dependent not only on the mass of saturated fat available but also on the number of double bonds formed per unit of mass.

The point at issue is not whether fat diets are superior to carbohydrate diets in the treatment of obesity, but that feeding carbohydrate for short periods reflects a tendency of the obese to retain body mass in the face of a deficit of food. However transient this tendency may be it emphasises the failure of the theory of indirect calorimetry to detect adaptive stresses which may occur in unsteady state of energy exchange during gain or loss in body mass.

Lyon et al.[2] observed R.Q.s below 0·7 in non-ketotic obese subjects fed on calorie-deficient low-carbohydrate diets, and the critical work of Benedict [3] on hibernating marmots revealed occasional similarly low R.Q.s. These workers attributed their findings to the theoretical introduction of oxygen into a portion of the fat molecule—namely, the net formation of carbohydrate from fat, which seems to me to be teleologically unsound. In the case of hibernation it would appear to be more reasonable for the animal to desaturate its body-fat stores in an attempt to keep cellular viscosity constant in the face of a falling environmental temperature, and a clue to this possibility lies in the finding by Fawcett and Lyman [4] of a rising iodine number in the depot fat of the hibernating hamster. Henriques and Hanson [5] demonstrated an inverse relationship between the iodine number of the fat of various animals at different sites and the temperature of its formation. They clearly showed that the iodine number of the depot fat of maize-fed pigs could be influenced not only by changing the temperature of their surroundings but also by cladding them in woollen pelts—i.e., by changing their micro-climate.

One may envisage the hydrogen atom as the shuttle on the loom of lipids, its removal from the molecule being an exothermic reaction leading to a decrease in viscosity if the environmental temperature is maintained, while its addition to the molecule is endothermic leading to an increase in viscosity. Lipids form an integral part of cellular membranes, particularly in the central nervous system, and it is interesting to speculate whether their alternate saturation-desaturation might play a key role in the permeability of living cells.

1. Dollery, C. T., Emslie-Smith, D., McMichael, J. *Lancet*, 1959, i, 296.
2. Turner, R., Lowther, C. *ibid.* p. 381.
3. Evanson, J. M., Sears, H. T. N. *ibid.* p. 544.
4. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., Rosenheim, M. L. *ibid.* p. 17.
5. Boura, A. L. A., Copp, F. C., Green, A. F. *Nature, Lond.* 1959, **184**, 70.
6. Boura, A. L. A., Green, A. F. *Brit. J. Pharmacol.* 1959, **14**, 536.
7. Gardner, W. J., Abdullah, A. F. *Amer. J. med. Sci.* 1955, **230**, 65.

1. Furnass, S. B. *J. Physiol.* 1959, **150**, 11 P.
2. Lyon, D. M., Dunlop, D. M., Stewart, C. P. *Biochem. J.* 1932, **26**, 1107.
3. Benedict, F. G., Lee, R. C. *Publ. Carnegie Inst.* 1938, no. 497, 1.
4. Fawcett, D. W., Lyman, C. P. *J. Physiol.* 1954, **126**, 235.
5. Henriques, V., Hanson, C. *Skan. Arch. Physiol.* 1901, **11**, 151.

At the birth of the theory of indirect calorimetry Lavoisier and De la Place [6] observed that the volume of carbon dioxide expired by a fasting man was less than the volume of oxygen consumed and that water was present in expired air. Lavoisier's logic led him to believe that some absorbed oxygen had combined with carbon to form carbon dioxide and some with hydrogen to form water. After Lavoisier's death organic chemists and workers in the field of animal metabolism formulated the hypothesis that animal heat could be explained on the basis of combustion of molecules, comparing living systems with the bomb calorimeter and ignoring the cellular synthesis which distinguishes the living from the non-living. Experimenters in intermediary metabolism emphasise reactions between molecules rather than between neighbouring atoms despite the fact that all "chemical" reactions are ultimately physical in nature. Surely, Sir, the time is ripe for logic to supplant experiment as the guiding force of scientific thought?

Medical Clinic,
Goulburn, New South Wales. S. B. FURNASS.

NATURE OF HYPERTENSION

SIR,—The findings reported by Dr. Perera in your issue of July 16 are extremely interesting. If it is indeed possible to divide persons into two practically non-overlapping groups of high and low diastolic pressure by the simple device of averaging five or more casual readings, or by taking the lowest of five or more, a great advance will have been made. Unfortunately it is not clear from Dr. Perera's letter what he has done. Is it his whole group of 1000 subjects which could be so divided, or is it the subgroups of 198 and 42? If it is the latter the result is not so impressive, since by definition the distribution of the lowest pressures of the 198 must lie entirely below 90 mm. Hg while that of the 42 must lie entirely above 90 mm. Hg and there can be no overlap.

Perhaps Dr. Perera would give more details of his findings, including the results in males and females, Negroes and whites, separately and showing that the distributions of number of recordings of pressure made are similar in his high- and low-pressure groups (for the lowest pressure found will of course decrease as the number of recordings made increases).

P. D. OLDHAM
J. A. FRASER ROBERTS
G. W. PICKERING
Llandough Hospital, G. S. C. SOWRY.
Penarth, Glamorgan.

BEDSORES OF THE GUT

SIR,—I should like to draw attention to a relevant and fundamentally important experiment (which has only just come to my notice) which further supports the view expressed in my letter of July 9.

In the abstracts [7] of the 44th annual meeting of the Federation of American Societies for Experimental Biology, held in Chicago 1960, R. Menguy recalls that it is generally thought that "stress" leads to gastric hypersecretion and ulceration. In his studies on albino rats submitted to stress, he found at the end of 20 hours that hæmorrhagic ulcerations were present in the gastric glandular mucosa of all of the stressed animals. Stomachs of the control rats were normal. In another series of experiments, in which pylorus ligation was performed, almost complete suppression of gastric secretion was uniformly observed in the stressed group of rats after six hours. He concluded that the development of gastric ulceration in the secretory mucosa of the rat during a non-specific stressful situation is accompanied by a decrease in gastric secretory activity.

London, W.1. J.-JACQUES SPIRA.

6. Lavoisier, A.-L., De la Place, P. S. *Hist. Acad. roy. Sci., Paris*, 1784, 355-408.
7. *Fed. Proc.* 1960, **19**, part I, 192(9).

MAGNESIUM DEFICIENCY AND TETANY IN KWASHIORKOR

SIR,—You recently drew attention [1] to the question of tetany associated with low serum-magnesium levels in man.

A form of calcium-resistant tetany has occasionally been seen in kwashiorkor. This has usually been a pre-terminal event in cases with severe electrolyte disturbance. Apart from typical carpopedal spasm there may be coarse tremors of parkinsonian type or generalised convulsions. The finding of severe magnesium deficiency in many cases of kwashiorkor [2] suggested this as a possible cause of the nervous disturbances.

The reality of the deficiency has been further confirmed by balance studies, and it appears that during the first few weeks of recovery infants with kwashiorkor may have a positive magnesium balance of the order of 50 mEq. In spite of this deficit, serum-magnesium levels are usually well maintained, the lowest figure in our original series being 1·33 mEq. per litre.

However, we have now seen three cases of calcium-resistant tetany whose serum-magnesium levels during tetany were 1·03, 1·23, and 1·40 mEq. per litre. One of those responded dramatically to intravenous magnesium after failure of calcium.

The case was an 8-month old infant with grave kwashiorkor. There was marked wasting, œdema, anæmia (hæmoglobin 5·1 g. per 100 ml.), hepatomegaly and hypoproteinæmia (serum-albumin 1·4, serum-globulin 1·9 g. per litre). Urine excretion of magnesium in the first 24 hours was 0·01 mEq. Other analytical figures are as follows (the specimen on day 0 was taken during tetany):

	Serum (mEq. per litre)						
	Mg	*Ca*	*Na*	*K*	*Cl*	CO_2	*pH*
Day −1	1·50	..	..	..	..	..	..
,, 0	1·23	5·1	114	5·1	88	14	7·35
,, +2	2·45	..	..	..	..	..	..
,, +3	1·95	4·1	114	3·8	80	15	..

An intermittent coarse tremor was noted on admission. The next morning obvious and typical tetany was present. Calcium gluconate (0·3 g.) was given intravenously but had no effect. The tetany in fact passed into generalised convulsions. 90 minutes after the calcium, magnesium sulphate (0·5 g.) was given intravenously, and within 30 seconds convulsions had ceased and there was complete relief of all muscle spasticity. The child yawned twice and remained quiet, flaccid, but conscious. The spasms recurred less severely 3 hours later and responded equally promptly to a further 0·5 g. of magnesium sulphate. There were no further episodes. On the 4th day, when the child had already received 12 mEq. of magnesium parenterally and 18 mEq. orally, muscle biopsy showed a magnesium content of 9·6 mEq. per kg. wet weight (normal 16–18 mEq.).

We need to know more about these episodes, and how often they are due to magnesium deficiency. A marginal calcium state may be a factor—although the total serum-calcium levels in this case do not imply any lack of free Ca^{++}, especially in view of the low albumin level of 1·4 g. per litre. Hydræmia during treatment might serve to bring the serum-electrolyte concentrations to a critical point. The effects of calcium and magnesium cannot be merely additive, in view of the failure of calcium treatment. Wacker and Ulmer [3] have shown that administration of the one may increase loss of the other from the serum.

It seems that magnesium deficiency in kwashiorkor does not often give rise to a low serum-magnesium level, but that if it does tetany may occur. The importance of magnesium treatment is that it may work.

M.R.C.
Tropical Metabolism Research Unit, R. D. MONTGOMERY.
Jamaica.

1. *Lancet*, 1960, i, 1232.
2. Montgomery, R. D. *ibid.* July 9, 1960, p. 74.
3. Wacker, W. E. C., Ulmer, D. D. *J. clin. Invest.* 1960, **39**, 1038.

HOSPITAL DESIGN

SIR,—I note that in your annotation of July 16 you ask "Why is the 36-bed ward of the Bellshill Maternity Hospital served by only two bathrooms?" As I was the senior medical person involved in submitting the requirements for the ward units in the hospital during the planning stage, I feel it is my duty to answer this question in fairness to my colleagues who were also involved in the planning.

You did not mention that in addition to the two bathrooms there are four showers making a total of six major ablutionary arrangements available to the forty-bedded ward unit. Incidentally, the standard ward unit is of forty beds not of thirty-six, as you stated. The installation of showers instead of bathrooms was largely at my insistence as I feel they have many advantages in a maternity hospital. They are more hygienic, can be cleaned with much less labour than a bath, and are much more comfortable to use for antenatal patients and for patients with perineal stitches. We have recently in this hospital installed a shower in a small eight-bedded lying-in ward. The patients have, on an average, some two showers a day and are very pleased with the arrangement, the vast majority preferring it to the conventional type of bath.

I trust that this will make the ablutionary arrangements in the new Bellshill Maternity Hospital clear. I still feel reasonably "enlightened" regarding patients' ablutions in hospital.

Maternity Hospital,
Bellshill,
Lanarkshire.

ROBERT A. TENNENT.

THE DIAGNOSIS OF AMYLOIDOSIS

SIR,—It seems in my last communication (June 18) I gave the impression that the tests described by Dr. Jarnum were not likely to prove helpful in the diagnosis of amyloidosis. This was not intended, but with due deference I would suggest a few subtle modifications would enhance their value greatly.

Evans-blue is a satisfactory agent in plasma-volume estimations only if certain strict principles are adhered to (these were described by Gregersen and Rawson [1]). They stressed that the accepted means of arriving at the initial concentration of the dye depends on a graphic analysis of the time-concentration curve on a semi-log plot with back extrapolation. Thus, it would seem preferable in Dr. Jarnum's proposed test to take 7–8 samples of blood in a period of 30 minutes following injection, with the inclusion of 4 of these samples in the first 10 minutes. The concentration at zero can be derived by extrapolation as demonstrated by Unger et al.[2] Loss of over 15% of the dye in the first 30 minutes would suggest amyloidosis.

I must take issue with certain other statements of Dr. Jarnum in his letter of July 2. I claim no originality for the observation that mixing of a dye is incomplete for 8–10 minutes in most persons. Numerous references to this exist.[3–5] He also states that the use of T 1824 and tagged albumin ^{131}I in estimating plasma-volume measure the same characteristics and give results which do not differe significantly. Overall and Williams [6] point out that this is not so, although I do not think this will affect the validity of Dr. Jarnum's second test.

Lastly, one other point is the possibility of a leak of Evans-blue in the urine of nephrotics as this dye is closely bound to the albumin function. I had formerly believed that congo-red did not pass into the urine in any significant amount and indeed had estimated the urinary loss of dye in several nephrotics confirming this for the most part. Lately, one patient with a high serum loss of congo-red demonstrated gross urinary leakage of the dye. She was a nephrotic who did not seem to differ in any obvious way from the other nephrotics tested.

University of Maryland
School of Medicine,
Baltimore.

WILLIAM K. C. MORGAN.

1. Gregersen, M. I., Rawson, R. A. *Physiol. Rev.* 1959, **39**, 307.
2. Unger, P. N., Zuckerbrod, M., Beck, G. J., Steele, J. M. *J. clin. Invest.* 1948, **27**, 111.
3. Gregersen, M. I. *in* Macleod's Physiology in Modern Medicine. St. Louis, 1938.
4. Gibson, J. G., 2nd, Evans, W. A., Jr. *J. clin. Invest.* 1937, **16**, 317.
5. Price, P. B., Longmire, W. P. *Bull. Johns Hopk. Hosp.* 1942, **71**, 51.
6. Overall, J. E., Williams, C. M. *J. Lab. clin. Med.* 1959, **54**, 186.

THE HARVEST MITE

SIR,—I have seen so many hundreds of individuals who claim never to be bitten but who are normally attractive and bitten frequently, without giving any recognisable skin reaction, that I would be happy to take on a bet with Dr. Nelson (July 16), and to give him odds of at least 100 to 1, that I could prove by experiment that his wife is as attractive (to mites) as many of his more sensitive patients.

The biting appendages of most arthropods are so small that in comparison the finest hypodermic needle is of the calibre of a city's main sewer pipe, so it is not surprising that the puncture is difficult to find if there is no reaction to the saliva. I myself have been bitten frequently and successfully by "clegs" (Tabanidæ) in the last few days. These raised horrid weals on some of my companions; even with a hand-lens I cannot, after 24 hours, find where some of them bit me. This surprised even me, for clegs are anatomically much grosser than many blood-sucking insects.

It is not always realised than sensitivity to arthropods, though unpleasant, is in part protective. The man who does not react to the presence of Sarcoptes (the itch mite) may support a large population in his skin, and be a danger to his contacts, while the man with severe clinical scabies often carries few parasites, for his fingernails may have almost disinfested him. The man who says he is "never bitten" may feed far more mosquitoes than the man who gives a severe reaction; the latter is aware of the insects, and flaps about and keeps them at bay.

Rothamsted Experimental Station,
Harpenden, Herts.

K. MELLANBY.

SIR,—When I practised in the wilds of Cornwall I used to suffer the torture of the damned with the irritation at night, but I saw in one of the journals that if one soaped one's feet and legs with plain carbolic soap and the inside of one's socks all would be well. It worked like magic and I was never troubled again.

Alcester.

C. C. H. CHAVASSE.

INTRATHECAL PHENOL

SIR,—Recent descriptions of the use of intrathecal phenol in the relief of pain and spasticity have stressed the safety of the procedure and the fact that it is not distressing to the patient.[1] Liversedge and Maher [2] more recently have emphasised the hazard of disturbance of the urinary bladder and sphincter. This has been the experience in this unit—particularly in patients who previously had had transient and often slight upsets of micturition. One patient, however, has experienced very unpleasant after-effects.

Aged 64, he had had disseminated sclerosis for more than twenty years and was treated for the relief of painful spasms of the legs. Using the technique described,[3] 1·5 ml. of 2% phenol in glycerol was injected at the L3–4 space with immediate relief of the spasticity. Half an hour later, as the superficial anæsthetic effect wore off, he began to have extremely violent flexor spasms, with the pain severe enough to make this otherwise stoical man scream out loud.

The pain was relieved with intramuscular pethidine 100 mg., and apart from a dull ache in both legs for the next two or

1. Kelly, R. E., Gautier-Smith, P. C. *Lancet*, 1959, ii, 1102.
2. Liversedge, L. A., Maher, R. M. *Brit. med. J.* 1960, ii, 31.
3. Nathan, P. W. *Lancet*, 1959, ii, 1099.

three days, there was no recurrence. Freedom from painful spasms has been maintained for three months. Further samples of phenol from the same batch have been used with no untoward effects and this has been a solitary experience in a series of fifteen injections.

Department of Neurology,
Northern General Hospital,
Edinburgh. IVAN T. DRAPER.

MEDICAL SUPERINTENDENTS

SIR,—Dr. Oldham (June 25) and Dr. Gilsenan (July 2) are prominent members of the group dedicated to representing the views of some clinical psychiatrists. The group might command more respect and active support for the worthwhile part of its programme if it appeared less narrowly dedicated to flogging medical superintendents.

There are clinical psychiatrists who believe that the medical superintendent still has a part to play and who do not begrudge him the £250 for the job.

R. CHAMBERS
Horton Road Hospital,
Gloucester. J. LOMAS.

"CHILD MOTHERS"

SIR,—The increasing number of young girls who become mothers and the incidence of venereal disease among adolescents to which you refer (July 16, p. 140) will hardly come as a surprise to those who are familiar with the problems of youth, but not everybody, I hope, would agree with your rather fatalistic conclusion that "physical maturity is thrust upon them at a time which is inconvenient, but *may be biologically appropriate*" (my italics).

While statistics show a tendency towards increase in body growth there is actually very little evidence that the young people of today have a stronger sex drive than their fathers and mothers had when they were young. Even if this were so there is nothing to support a contention that childbearing at such a young age is biologically appropriate. On the contrary, physiological evidence suggests that young girls are not physically ready to bear children, and from a psychological point of view there is everything against an immature adolescent becoming mother to a child. I agree that the methods of instructing in school about the facts of procreation may be out of date, as the youngster of today has no other means of informing himself without detriment to his morality. Sex education in school has always been hampered by the fact that teachers have to explain an emotionally laden topic in an unnaturally casual way to a group of children of varying sexual maturity, because the parents, upon whom the onus for dealing individually with such a personal matter should rest, are too readily delegating an embarrassing duty. It may also be necessary to review some of our guiding concepts of sex education, in the light of recent experience, as they are still largely based on doctrines established near the turn of the century, when Freudian teachings were a boon to the repressed and guilt-ridden masturbator or the neurotic love-sick maiden full of complexes, who, thanks to these courageous pronouncements, hardly exist any more. Perhaps Freudian concepts, once so revolutionary and ultra-modern, have become obsolete during the last sixty years of rapid scientific development and are out of touch with the requirements of modern sex education.

The modern unfortunate victims of their uncontrolled sex drives are not disturbed and hardly ever seen at the child-guidance clinic before they get into trouble, but they are confused by the bewildering prevailing moral codes and the contradictions in present-day philosophies. Young people need more instruction about the sanctity of life and consideration for the newborn baby than about the physiology and technique of intercourse. If young people could be made aware of the unhappiness their thoughtless acts can cause the children thus born to parents not yet ready and prepared to devote themselves to motherhood, I am sure these impetuous but impressionable adolescents would think twice before exposing themselves to such consequences. They would certainly profit from some instruction about the emotional needs of the infant and the danger of growing up without enduring mother love, quite apart from an explanation of the social advantages of the sanctity of marriage.

Perhaps it would be appropriate to conclude with the observations of Dr. Alex Comfort in the opening article in your same issue, that "there seem to be too few common-rooms in which working biologists and working psychoanalysts can come into daily contact, or even collision". One might only want to add that in the interest of our young people, teachers and sociologists should also be invited.

A. K. GRAF
Medical Director,
Leicester. Leicester City and County Child Guidance Services.

THE CAUSE OF OEDEMA IN "COR PULMONALE"

SIR,—We are grateful to Dr. Polak and his colleagues (July 16) for their expert marshalling of the evidence that experimentally induced hypercapnœa in man and animals does not cause net sodium retention. We were unaware, at the time we wrote our paper (May 28), of their observations in dogs extending over periods of up to eight days. We had relied on the fact that most, if not all, patients tolerate hypercapnœa for months or years without developing œdema when we stated that "the pCO_2 may be raised without œdema being present". Before writing the article we concluded from this evidence that hypercapnœa per se cannot be the cause of œdema in cor pulmonale. We suggest that the development of œdema in hypercapnœa depends on interaction with other mechanisms, the clue to which may lie in the factors governing the renal behaviour described by Dr. Polak and his colleagues. It might be relevant that all the circumstances listed by Dr. Polak and his colleagues probably involve hyperventilation: most, if not all, of the clinical conditions in which we noted a coincidence of hypercapnœa and œdema are characterised by hypoventilation.

Department of Medicine,
The Middlesex Hospital,
London, W.1. E. J. MORAN CAMPBELL.
Aberdeen Royal Infirmary. D. S. SHORT.

ORAL HYPOGLYCÆMIC AGENTS

SIR,—It would be most unfortunate if Dr. Dolger's strictures (July 16) on chlorpropamide obscured the fact that it is a most effective and useful hypoglycæmic agent. It has the enormous advantage over tolbutamide that it is effective in a single daily dose in contrast to the three or four doses of tolbutamide often recommended. I trust that Dr. Dolger has never required to take medicine three or four times per day, but if he has he must agree that although the morning dose is easily remembered subsequent doses may often be forgotten.

We have used chlorpropamide in more than 350 cases during the past two years and so far have encountered no toxic manifestations. Dr. Dolger draws attention to the incidence of jaundice in patients treated with chlorpropamide. Despite the allegation that this is an idiosyncrasy to the drug the possibility that it is dose-related cannot be dismissed. It is certainly necessary to emphasise the desirability of giving this drug in the minimal effective dosage, as must always be the consideration with any potent therapeutic agent. We always recommend that where a satisfactory response is observed the dose should be reduced, and consideration should then be given to whether continuous therapy is necessary. We believe that this applies equally in the use of other hypoglycæmic drugs. The very fact that tolbutamide is widely stated to have no toxicity

may lead to this drug being prescribed somewhat unnecessarily to patients who should be capable of diabetic control by diet alone, or it may be continued without adequate subsequent supervision when relaxation of dietary care may largely invalidate it, or its administration may be continued when in fact it is no longer required.

The Victoria Infirmary, Glasgow.

IAN MURRAY
M. J. RIDDELL.

THE FEMALE PROSTATE

SIR,—Mr. Moore, in his admirable and friendly letter of July 23, mentions the difficulties of diagnosis in differentiating between bladder-neck obstruction and other forms of dysuria in women. I agree with him that on clinical examination in some cases doubts may outlast the most exhaustive investigation were it not for a simple test which I have found helpful.

If 1 ml. of carbachol is injected into a woman with bladder-neck obstruction she will immediately go into complete retention of urine demanding relief by catheterisation. In the other conditions which simulate "female prostatic obstruction" the injection of carbachol will result in the bladder being emptied.

London, W.1. W. SKYRME REES.

THE INEFFECTIVE TOOTHBRUSH

SIR,—The toothbrush fails as a machine because teeth are not rigid structures fixed rigidly in bone, but on the contrary they are rigid structures sitting in an elastic bed on the bone. Food debris that has become impacted between teeth can only be removed by the use of a force sufficient to overcome the elasticity of the periodontal membrane, and for that reason the toothpick must always be more efficient than any bristle yet devised.

There is a serious lack of evidence that toothbrushing has any beneficial effect on dental caries. Investigations in this country suggest that schoolgirls with their greater interest in the cosmetic value of the toothbrush are almost twice as conscientious toothbrushers as schoolboys—but the schoolboy often has better teeth.

The failure of the toothbrush to remove impacted putrifying food debris has been alleged to be a not uncommon cause of halitosis.[1] There is a need for a scientific assessment of the value of different methods of tooth-cleaning, and a field that might be usefully explored is the group of Commonwealth students in England who, in their childhood, may have practised many and varied forms of tooth-cleaning.

London, N.2. J. L. PATTON.

THE MALIGNED TOOTHBRUSH

SIR,—The fact that the design of the toothbrush has changed little in the past hundred and thirty years surely indicates that it has stood the test of experience. It is nonsense to assert that a brush is ineffective because it is misused, ill used, or not used at all. A bad workman blames his tools. When my wife hands me back an eggy spoon whilst I am washing up, is the mop, the water, or the detergent blameworthy?

Used with common sense, elbow grease, and a dentifrice the toothbrush is a very efficient toilet article. It ought to be very much cheaper to buy.

The toothbrusher can be encouraged to look at what he is doing by using a mirror. He does when he is shaving, and so does she when she is putting on lipstick.

London, W.1. H. W. BREESE.

1. McGolrick, L. *Brit. med. J.* 1958, ii, 402.

AUTOLOGOUS GLIOMA TRANSPLANTATIONS

SIR,—As an experimentalist reading the preliminary communication in your issue of July 9, I was, to say the least of it, surprised that such experiments could have been inflicted on a human patient when so much past experimentation on animals in the laboratory had, some forty years ago, already shown what to expect. It is tragic that there could be such a divorce between the hospital ward and the research laboratory.

As far back as the early 1920s, it was known that autologous transplantation of a fragment of a spontaneous tumour was the best means of transplanting such a tumour. Moreover, it was abundantly proved by experiment that the growth of the autoplastic tumour in no way inhibited or caused regression in the remains of the primary spontaneous tumour.

In those early days much research was devoted to a study of spontaneous tumours in animals. Two problems were always present: was the tumour malignant, and was the tumour transplantable? A difficulty in connection with a diagnosis of malignancy was the great rarity of metastases, that infallible criterion of malignancy in man. This led to the habit of attempting to graft such spontaneous tumours, not only to answer this specific question but to obtain material for further study. In fact, if a new spontaneous tumour was produced for discussion at any of the learned societies a question was certain to be asked as to its transplantability. Thus in those days if one observed a spontaneous tumour in laboratory mice it was the practice to graft 100 mice with the tumour in the hopes of obtaining a few positive results, but much more often than not the grafts did not "take". This practice was therefore modified to autoplastic transplantation—that is to say, transplantation to some other region of the tumour host's body. It was found that in this way transplantation of the tumour was frequently successful, and, moreover, that grafting from such an autologous tumour could be effected in other animals, and thereafter with increasing success in succeeding transplantations.

A little later, when the experimental inductions of tumour was being studied by the application of coal tar or soot extracts to the skin, the question of the malignancy of the induced tumours was a matter of importance. In testing by grafting the tumours into other animals it was found that it was almost impossible to transplant such skin tumours into other hosts. However, autoplasty was generally successful, even with infected ulcerated tumours, probably because the animal could deal with its own low-grade infections. But in these autologous grafting experiments the primary tumour never regressed as a result of the growth of the transplants, nor, in my experience, did the failure of an autotransplant to grow induce a regression in the primary. The practice was to graft into the soft tissues of each axilla and groin, and the result was frequently a tumour in each site. But it was quite common for one or more of the grafts to fail to grow to tumour size, in which case this did not appear to inhibit the growth of the remaining grafts, nor of the original spontaneous tumour.

There remains another technical point: the authors mention the fact that glioma grafts in animals do not metastasise. This is in keeping with the observation that, in general, transplantable tumours in laboratory animals do not give rise to metastases. This is to be expected in that spontaneous tumours in laboratory animals do not readily metastasise. But that was no justification for supposing that this would hold good in man, because in man malignant tumours nearly always give rise to metastases, and in the event, as your contributors record, these autotransplants actually did spread to neighbouring lymph-nodes. Surely this alone is a sufficient reason for not continuing such experiments on the living man. What is the use of an antibody formation, which must be so trivial in amount as to give rise to no reduction in the host tumour, if the autoplasts are to result in metastases elsewhere? What could be more distressing for the patient, or do more to defeat the clinician?

If there is need to doubt the laboratory results in this branch of cancer research surely what is required is further work in the laboratory—certainly before experimentation on the living patient.

Finally, in removing a primary tumour every surgeon has surely had the unfortunate experience, some time in his life, of inadvertently grafting the tumour in or under the skin or elsewhere in the patient. Has such an unfortunate and involuntary autotransplantation ever given rise to a regression temporary, or complete, in the disease in that patient? Here we have the experiments already carried out, and the answer surely is " no ".

Chester Beatty Research Institute, London, S.W.3. R. D. PASSEY.

SIR,—In their paper of July 9 Dr. Bloom and his colleagues say that their patients gave " permission " for the experiment after the procedure had been " explained ". It is difficult to see how anything approaching an adequate " explanation " could evade the issue of prognosis. " Deprive no one of hope," said Osler. To this has now to be added, " unless you want permission to experiment upon your living patient ".

I suggest that this paper springs from that widespread inability of many who should know better, to realise that all biological experimentation, animal and human, no matter how intrinsically laudable, is subject to the limitations imposed by the humane, ethical, and moral codes by which most of us conduct our affairs. I am surprised that you thought fit to accept the paper.

Swansea. M. E. N. SMITH.

*** Whether Dr. Bloom and his colleagues were justified depends largely, in our view, on what was said to the patient and whether he wanted to volunteer. This can be fully known only to the doctors and patients concerned. Before accepting the paper we asked Dr. Bloom whether the additional tumours might increase the risk of fatal metastases. His reply convinced us that he and his colleagues had given this matter the grave consideration it deserved.—ED. L.

HOMOSEXUALITY

SIR,—Dr. Soddy's six columns (July 23) of naïve distress that Parliament and the public do not yet appreciate mutual masturbation, intra-crural and intra-anal intercourse, and fellatio (Norwood East and Hubert gave this as the order of frequency) as permissible forms of activity between adult men even in private reminds us that he gave 14 columns of instruction in the same subject some time ago, apparently without avail, and you, Sir, refused me space to reply.

If I and those who think as I do, the majority, thought there was the slightest chance of Dr. Soddy's views prevailing we should form a Labouchère Society to combat them. This gentleman's splendid amendment was not passed on a dark night when no-one was looking, as some of Dr. Soddy's friends aver, but after consultation with the then Home Secretary and Attorney-General, " both very experienced men " according to " Labby ", and with the almost unanimous assent of both Houses of Parliament. Almost certainly it was designed to deal with some homosexual dens that were thriving in London at that time and which would certainly crop up again if Clause 11 were annulled.

But the saddest part of Dr. Soddy's 22 columns is that they show he does not appreciate the natural history of the matter, nor, as far as I know, is there any appreciation of it in psychological literature. Research without knowing the natural history basis will be futile. If you will give me the space of about six columns and a month I am quite willing to enlighten him, but with your genius for monocular vision you probably won't.

Beckley, Rye. C. G. LEAROYD.

*** Dr. Learoyd's opinions on this subject must now be well known to our readers. Their further elaboration would not, we think, be helpful—ED. L.

" CUFF HYPERTENSION "

SIR,—I have read this correspondence with interest.

In order to obtain more accurate estimates of the blood-pressure in infants, I had cuffs made to special order some years ago by Chas. Thackray, 38, Welbeck Street, W.1. for use in the theatre and elsewhere at The Hospital for Sick Children, Great Ormond Street. These cuffs were made longer than those " normally " supplied for the reasons given by your correspondents.

The cuff 2 in. in width is normally only 4 in. long. I had this made 6 in. long. In addition I had another cuff made, $1^1/_2$ in. wide and 5 in. long. These longer cuffs have proved very much more satisfactory than the " standard " ones in practice.[1] My interest in cuffs for infants was stimulated by the fact that it is of particular importance to have accurate estimation of the blood-pressure when using hypotensive techniques during surgery in infancy and childhood.

The Hospital for Sick Children, London, W.C.1. SHEILA M. ANDERSON.

CARCINOGENICITY OF IRON-DEXTRAN COMPLEX

SIR,—I should like to associate myself with the remarks of Dr. Duthie and his colleagues (July 16).

It seems to me that there has been a quite unnecessary panic reaction over inconclusive animal experiments which bears little relation to clinical conditions. It is only when one contemplates abandoning intramuscular iron therapy that one appreciates the very important place it now fills in the treatment of the iron-depletion anæmias of early childhood.

I hope that the manufacturers will carefully consider the well-authenticated evidence of the great benefit which 'Imferon' has already brought to patients and set similar potential therapeutic effects in the future against the hypothetical neoplastic hazard now receiving so much publicity. May I urge them to continue marketing the product unless some less speculative evidence of possible carcinogenic properties in man is to hand?

I for one have continued, and will continue, to use intramuscular iron for children requiring this therapy.

Royal Hospital for Sick Children, Glasgow. GAVIN C. ARNEIL.

1. Anderson, F. M. *in* Evans, F. T., Gray, T. C. General Anæsthesia; vol II, p. 184, table v. London, 1960.

Appointments

EDMONDSON, MARGARET M., M.B. Edin.: assistant M.O., Brentford and Chiswick, Heston and Isleworth, and Southall, Middlesex.
EVANS, GWILYM, M.B., B.SC. Wales: M.O., Welsh Regional Hospital Board.
HORSLEY, J. S., M.R.C.S.: senior M.O. for mental health, Sheffield.
LAVIS, PETER, M.B. St. And., D.P.H.: deputy M.O.H. and deputy school M.O., Bedford.
MACDONALD, I. J., M.B. Lond., D.P.M.: part-time assistant (S.H.M.O.) in the psychiatric department, St. George's Hospital, London.
MCGREGOR, C. M., M.B. Cantab.: assistant M.O.H. and school M.O., Wolverhampton.
PEARCE, ARNOLD, M.B. Lond., D.P.M.: assistant psychiatrist (S.H.M.O.), Park Prewett Hospital, Basingstoke.
REID, J. T. W., M.B. Glasg., D.P.H.: deputy principal school M.O., Durham.
ROBERTS, D. J., M.B. Cantab., D.P.H.: deputy M.O.H. and deputy school M.O., Southport.
SHAW, KATHLEEN, J. C., M.B. Edin., D.C.H.: senior M.O. (maternity and child welfare), Leicester.
THORPE, G. R., M.B. Lpool, D.P.H.: assistant M.O. and M.O.H., Louth, Mablethorpe, and Sutton, Lincolnshire.

Parliament

Hospital Progress

ON July 21 Dr. EDITH SUMMERSKILL took the opportunity of a vote on the supplementary estimates to discuss the hospital service. Over the years she had been left with the impression that the approach of the Minister to the National Health Service was completely haphazard and lacking in coordinated policy. Only when coordination between the three parts of the N.H.S. had been secured and the emphasis placed on preventive work and the domiciliary services, would the hospitals be used intelligently and economically. Long waiting-lists were in part due to the failure to coordinate the local services, and the hospital waiting-lists had risen to 476,000 at the end of 1959—33,000 more than the year before. The Minister told the House time after time how the poliomyelitis service was developing. But what of other preventive work? Was there coordination between his department, the Ministry of Labour, and the Home Office on the occupational diseases? The incidence of bronchitis, particularly in industrial areas, was very high. The new town of Harlow had the highest birth-rate in the country, yet still it had no special accommodation for its maternity cases. No doubt, greater attention would now be paid to the lack of adequate accommodation and the failure fully to implement the Cranbrook report since the report on inquiries into maternal deaths. What was being done to protect the public from the inexperienced doctor who was told to deputise for his superior? In her view, the public was entitled to a periodic inspection of the quality of medical care in our hospitals. The Minister had also failed to provide adequate facilities in hospitals for the training of dentists. The minimum proportion of dentists needed was estimated at 1 to 3000 children. At present the average was 1 to 7000.

She hoped that the Minister would not suggest that these failures of administration were due to the parsimony of the Treasury. Everything she had mentioned could be traced to a lack of planning, a failure to recognise priorities, and the absence of a positive and vigorous lead. The Minister should not plead a shortage of money when he allowed such a wastage of public money on drugs. Every year since the Minister had been in office, the drug bill had increased. The total cost in hospital and outside was now £86 million. The Comptroller and Auditor General said that the profits of the drug firms, and especially the American-controlled firms, were well above the average for general industry. In 1957, the drug manufacturers came to a three-year agreement with the Ministry. It had completely failed. The cost of prescriptions has risen every year. Each time she had ventilated this outrageous exploitation of the National Health Service, the Minister had assured her that he would make an announcement when the three-year agreement ended this month. Was it really the fact that he had promised the "vultures of the pharmaceutical industry yet another six months in which to make their unholy profits at the expense of the community"? Again the Minister deplored the shortage of practising midwives, mental nurses, and radiographers yet he had failed consistently over the years to anticipate these shortages, which arose because of the bad conditions and low pay. There was clear evidence of a deterioration in the National Health Service, owing to a failure to integrate the service, to recognise priorities, and to check results by the effects on the patients themselves.

Lord BALNIEL pointed out that the expenditure on new hospital buildings had increased from £10 million in 1955–56 to £31 million next year. He thought that all those interested in health heaved a sigh of relief at the knowledge that priority, which for many years was rightly focused on housing and education, had at last been widened to include the hospital service. But the shift of emphasis had not come too soon. He doubted whether anyone had much idea what, in the present affluence of the country, was the correct capital programme for hospital building. There had not been a national survey of our hospital needs since the survey made during the war. If we insisted on more money being spent on hospital building, we had a duty to examine the administrative structure by which the hospitals were built and to make certain that we got the very best value for our money. In particular, we should look at the two authorities charged with the responsibility of building hospitals, the Ministry and the regional boards. We must try to reach a fair balance between these two authorities, to achieve, on the one hand, efficiency and rapidity of building and, on the other, responsibility to Parliament and control of cost. He had himself seen the building of a hospital held up for a year while pathetic little plans for pathetic little matters were shuffled about between the Ministry and the board. He would like to see the Ministry given far greater autonomy by the Treasury, and the regional boards given far greater autonomy in the management of their own affairs, and the hospital management committees in theirs.

If we left greater control in the hands of the regional boards we should get much greater individuality in the designs of our hospitals; but, if we were to achieve a large hospital building programme we must at the same time be prepared to accept some basic designs on the lines of successful standardisation in the school-building programme under the Ministry of Education. He would like to see the day approaching when any regional board building a hospital could turn to the Ministry for a readymade design for an outpatient department. Had the Minister given thought to the possibility of exchanging staff between the hospital authorities and the Ministry, somewhat on the lines of the exchange of staff between the Colonial Office and the administrative officers in the field? The Ministry of Health was rather different from most Ministries. It was directly running one of the largest organisations in the country. To increase the understanding between the Ministry and the regional boards, an interchange of staff should be considered even if it involved a substantial constitutional change.

Mr. LAURENCE PAVITT believed that steps should be taken to secure greater integration of general practitioners and the local health authorities with hospitals. Pathological, X-ray, and sterile-syringe services had been made available to general practitioners in the vicinity of Chadwell Heath Hospital in Essex and were used in about a dozen practices. Since their inception references to outpatient departments by these doctors had been cut down by half. A similar scheme at the Nelson Hospital, Merton, had to be stopped because radiographers were not available. It was up to the Minister to clear up difficulties due to shortage of staff. The Minister should also tackle the problem of the huge chasm between the highly developed teaching hospitals and the broad mass of hospitals under regional boards which were taking the bulk of medical work on their shoulders. The regional hospitals were in the majority, but the top consultants from teaching hospitals were the people who more or less imposed their will over the whole of the Service.

Mr. KENNETH ROBINSON said that, expressed as a percentage of the gross national product, the cost of the National Health Service today was still substantially below that of 1950. But he wished to draw attention to some shortcomings which could be put right without the expenditure of a single £1. The hospital service received from the Ministry plenty of detailed guidance. Some of it was good, some less good. Circulars fell like the leaves in Vallombrosa. But there seemed to be little or no forward thinking, no policy-making, and marked indecisiveness where decision was needed. For instance the Mental Health Act envisaged a fairly rapid development of psychiatric units in general hospitals. Among doctors in general hospitals there was undoubtedly a marked prejudice against psychiatry. There would be a prejudice against setting up these units unless pressure was exercised by regional boards, and, by the Minister himself. There was little sign so far that any such initiative was forthcoming. Again the Minister tended to regard himself as a reconciler of interests in the service. In this he showed himself excessively tender towards the medical interest. Mr. Robinson agreed that a Ministry which was having a perpetual running battle with the medical profession probably would not result in a particularly efficient hospital service, but where there was a conflict between the interests of

the patients and the interests of the doctors it was the duty of the Minister to see that the interests of the patients prevailed. This was not by any means always done. The Minister knew that the Cranbrook Committee was right in insisting on an obstetric list with definite qualifications, and a list which was kept regularly up to date. He could have insisted on the implementation of this recommendation, instead of which, because the British Medical Association objected for some misconceived notion of professional prestige, nothing had been done for fifteen months. Another complaint often heard in the House was about the minority of part-time consultants who were not doing the work for which they were being paid. They were leaving to their registrars far too many duties. Other common complaints—again, about the small minority of consultants—was the way in which they persuade patients to undergo treatment privately in order to get some sort of priority for a bed in a hospital.

Mr. DEREK WALKER-SMITH agreed that the National Health Service was a very large-scale industry. They had 2641 hospitals and over 7000 consultants in those hospitals, about 12,000 other doctors, 194,000 nurses and 12,000 midwives, and about 233,000 other employees. They spent over £400 million a year. This large-scale enterprise was inevitably labouring under some inherited disadvantages, such as old buildings and inconvenient sites. They were seeking to remedy these things by extension and modernisation and building new hospitals. Meanwhile a good deal of the work was necessarily done in difficult conditions. He agreed that the waiting-list figure was higher. It imposed two clear duties on us: to operate a fair system of admission and to improve our methods and expand our accommodation. But if we considered these waiting lists as illustrating the problems in the hospital service, we must also have regard to the other side of the picture—the increased volume of work. Last year, we achieved 4 million courses of inpatient treatment—an increase of 3% on 1958. In the past four years, we had increased the number of attendances at outpatient clinics from 37 million to 41¼ million. These figures reflected the shift of emphasis from institutional care to care within the community. There were now nearly 400 psychiatric outpatient clinics at general hospitals and about 70 day hospitals.

Turning to the report on maternal deaths, he said that though there were cases where elementary precautions were not taken and serious mistakes were made not all the avoidable factors were of this kind. One of the commonest was failure by the patient or her family to take the advice given or even not to seek professional care. We must also have in mind the scope of the report. It dealt with 861 maternal deaths directly due to childbirth in a period when there were 1112 such deaths but more than 2 million births. The report showed a decrease in maternal deaths of more than a fifth since the first report was published in 1957, and that despite a rising birth-rate.

Progress had been made in applying in the hospital service a system of pay and conditions reflecting appropriate comparability with work in other walks of life and providing an appropriate career structure, and this had been reflected in the figures of recruitment for midwives and nurses. The programme of hospital building had gathered pace. By the beginning of this year we had 180 major hospital schemes at varying stages of building or planning. We had 8 new hospitals partly completed and partly brought into use. We had 9 new hospitals started, and we had 17 new hospitals at planning stage.

New Plans for Research

On July 19 Lord TAYLOR asked H.M. Government whether any progress had been made towards setting up a hospital or special centre for clinical research; and whether any further progress had been made in the provision for research in tropical medicine.—Lord ST. OSWALD replied: The Medical Research Council's report for 1958–59 [1] contains details of the proposed clinical research centre and of a new Tropical Medicine Research Board. The Council have appointed Prof. J. R. Squire, who at present holds the chair of experimental pathology at Birmingham University and is honorary director of the Council's unit for research on the experimental pathology of the skin, to take charge of the clinical research centre and to advise on its design and organisation and on the selection of a suitable hospital in which it can be incorporated.

It has been agreed that the Council should take over responsibility for coordinating and promoting research in tropical medicine supported from public funds, and it is to advise them in these matters that they propose to set up the Board. The Overseas Research Council, which is responsible for general policy on overseas research, has concurred in the proposals. The new Board will also take over the work of the Colonial Medical Research Committee which will be dissolved. It will advise the Secretary of State for the Colonies, through the Medical Research Council, on all medical research in or for the Colonies financed from Colonial Development and Welfare Funds.

Lord TAYLOR: May I take it that the establishment of this new centre will not lead to any reduction in other clinical research being done, or to a reduction in expenditure? May also I take it that the establishment of the Board will enable research to be carried out in Commonwealth countries, as well as in Colonial territories, and that there will be a career structure for doctors working in these services?—Lord ST. OSWALD: I am happy to say that the noble Lord is correct in both his assumptions. The centre will be an addition to, and not a substitute for, the Council's normal methods of supporting research, such as the establishment of individual research units and the award of research grants and travelling fellowships. Since the war the Colonial Medical Research Committee has advised on the research which should be undertaken with support from Colonial Development and Welfare Funds. Because an increasing number of overseas territories are passing from Colonial to independent status and leaving the ægis of the Colonial Office, they cease to be eligible for aid from Colonial Development and Welfare Funds. The organisation of research in the tropics has therefore had to be reconsidered. It is hoped that by providing, under the auspices of the Board, a career structure which will enable interested research-workers to devote themselves to tropical medicine, the experience, knowledge and resources of modern medical research may be brought to bear on problems of disease in this field, and that cooperation with tropical countries will thereby be facilitated. Lord TAYLOR: Tropical countries outside the Commonwealth as well? Lord ST. OSWALD: I cannot give a specific answer on that point, but I have no reason to think that it will be restricted to the Commonwealth.

QUESTION TIME

Nuffield Grant for Industrial Health Service

In reply to a question, Mr. EDWARD HEATH, the Minister of Labour, announced that the Trustees of the Nuffield Foundation had allocated £250,000 for the further development of group industrial health services and industrial hygiene services. The money would be applied to assist practical schemes which promised to be self-supporting after an initial period of development. In the selection of such schemes, the Foundation would work in close cooperation with his department.

Emergency Calls

Mr. JAMES DEMPSEY asked the Postmaster-General if he would post the names and telephone numbers of local doctors in a conspicuous part of telephone kiosks for the convenience of the general public.—Mr. J. R. BEVINS replied: I have recently arranged for lists of National Health Service doctors to be available in telephone exchanges so that inquiries from both kiosks and private telephones can be dealt with. These lists are also held at the larger Post Offices. I believe that these arrangements, and the 999 service, provide the best way of meeting this public need.

Mr. W. R. WILLIAMS: Can the Minister arrange to have a notice in the kiosk to say that the names of doctors in the vicinity can be obtained on application to the telephone exchange?—Mr. BEVINS: There is not much room in kiosks for this sort of thing, but I will consider the suggestion.

1. See *Lancet*, July 23, 1960, p. 193.

Notes and News

EDITORIAL PSYCHIATRY

BELYING the impression gained, doubtless, by many failed contributors, Dr. Harvey A. Robinson, managing editor of the American *Journal of Nervous and Mental Disease*, presented a genial account of his work to the Royal Medico-Psychological Association on July 12. His monthly journal, which is widely read overseas, required of him four days' work a week (though he remained associate professor in the Maryland School of Medicine). Founded in 1874 (second oldest of its type in the U.S.A.) the journal tried to balance articles from all disciplines concerned with psychiatry, but the readership was never satisfied. About 70% of the articles submitted were rejected and changes were almost always called for in the remainder. Good articles often came from an unknown pen and bad ones from eminent seats of learning.

Dr. Robinson found much to deplore in the current scene. The pressure on workers, especially in the U.S.A., to publish (promotion and even security of tenure depended on it) resulted in poor work, repetitious publication, needless expansion of a single topic to three or more papers, and the proliferation in modern times of more and more mediocre scientific periodicals. There were too many of these and libraries were being filled with bound volumes of junk. He deplored too the custom whereby the director of any department added his name to work by his juniors of which he knew nothing. The real authors knew they were being exploited but could do nothing about it. These patterns arise, he thought, from deep roots within the competitive educational system. This urge to publish frequently resulted, too, in many small ill-digested projects, where science would have been better served by a more concentrated endeavour upon a larger theme. It was very sad that the forthright statement had gone out. To avoid challenge, writers were prepared to hedge and to equivocate, and to go to great lengths in order to document the obvious. The polemic of the great public controversies of the past had gone, and Dr. Robinson doubted we had gained thereby. Together with this refusal to criticise went a refusal to admit ignorance: juniors, especially, were not permitted to say they did not know.

The editorial referee was in a unique position. He was able, secure in anonymity, to give forthright views and criticisms (or unequivocal praise) to papers submitted to him, and Dr. Robinson thought it very important to give authors useful advice, since, in the U.S.A. anyway, training in scientific method and statistical technique was hard to come by. His task as editor was that of a somewhat uneasy intermediary, though as a whole he had found it a most rewarding experience.

QUEEN SUBSTANCE

Dr. R. K. Callow and Miss Norah Johnston, of the National Institute for Medical Research, have succeeded in identifying and synthesising the "queen substance" which controls reproduction in honeybee colonies. This substance, produced in the mandibular glands of the queen bee, is obtained by the worker bees which look after her, and it is distributed by them throughout the colony. It prevents the workers from raising any new queens.

For some years Dr. Callow and Miss Johnston have been collaborating with Dr. C. G. Butler of Rothamsted Experimental Station, and their new findings appear in the June issue of *Bee World*, the journal of the Bee Research Association. They have ascertained that queen substance is 9-oxodec-2-enoic acid.

This work, the Association says, "offers beekeepers the prospect that swarming may one day be controlled. Since the production of new queens during swarm preparations is presumably due to a deficiency of queen substance, then feeding queen substance may perhaps prevent colonies from swarming".

University of Oxford

On July 9 the following degrees were conferred:

D.M.—D. W. K. Kay.

B.M.—D. M. Hill, John Hodgson, R. E. Sadgrove, P. R. Wilson, Clarence Williams, R. L. Carter, D. J. Lane, G. M. R. Smith, W. L. Armstrong, J. L. Lane, A. J. Sandford, J. G. C. Surridge, D. G. Evans, C. W. K. H. Greaves, Jonathan Brostoff, J. M. Rice Edwards, M. J. Parkinson, R. M. P. Reynolds, C. G. Jones, Celia Harvatt, Giovanna C. F. Karlsbad, Ann-Mary G. Lewis, P. G. Lynch, P. S. Vickers, C. W. Burke, Irene M. Jolles, David Barnett (in absentia).

University of London

Dr. C. B. B. Downman, reader in physiology at the Royal Free Hospital School of Medicine, has been appointed to the Sophia Jex-Blake chair of physiology at that school.

Dr. Downman graduated B.SC. Lond. in 1937. While continuing his medical studies he held a junior demonstratorship at St. Thomas's Hospital Medical School and spent some time as a student medical officer at the South-West London blood supply depot. After qualifying in 1941 he was appointed lecturer in physiology at St. Thomas's. In 1943 he was seconded for nine months to the National Institute for Medical Research and in 1948 he exchanged posts with the senior lecturer in the department of physiology in the University of Otago. He obtained the degree of PH.D. in 1953. He took up his present appointment at the Royal Free in 1954. His published work includes papers on the physiology of the vascular and nervous systems.

The title of professor emeritus of surgery has been conferred on Sir James Paterson Ross on his retirement from the chair of surgery at St. Bartholomew's Hospital Medical College, the title of professor emeritus of morbid anatomy on Dr. Dorothy Russell on her retirement from the chair of morbid anatomy at the London Hospital Medical College, and the title of professor emeritus of bacteriology on Dr. Wilson Smith on his retirement from the chair of bacteriology at University College Hospital Medical School.

University of St. Andrews

Dr. E. R. Alexander has been appointed assistant in physiology in the department of physiology and biochemistry, Queen's College, Dundee.

University of Edinburgh

On July 20 the following degrees were conferred:

M.D.—S. G. F. Wilson (highly commended); Boleslaw Bendkowski.

Ch.M.—G. F. Murnaghan (highly commended).

Ph.D. (in the faculty of medicine)—J. F. Lamb.

M.B., Ch.B.—Isobel R. Card, W. L. Ford, G. E. Mawer, J. F. Munro (with honours); P. J. Abernethy, J. G. Adamson, C. I. Aitchison, Fereydoun Abolghassem Ala, Frank Alcock, D. H. T. Bain, Annis H. Belbin, Harvey Bertfield, I. J. Black, W. M. Bowden, A. W. Brewis, Margaret L. Brownlee, Sylvia A Camp, R. J. Campbell, Bernard Canavan, Eleanor R. Chalmers, Philip Cheh See-yave, D. J. Clark, J. G. Clark, D. J. Clarke, Malcolm Cooper, G. N. Crookes, Sheila M. B. Donald, M. L. Dorfman, W. H. Duthie, N. St. J. P. Dwyer, Jenny Eastwood, M. A. Eastwood, J. N. Edgley, T. E. Escott, K. W. Fairhurst, R. H. Farrow, D. M. Flynn, R. E. Fraser, C. A. S. Galloway, J. M. D. Galloway, Mary W. Gibson, Elizabeth D. Glover, Janet M. Gray, Yvvonne H. Green, William Groundwater, Bridget M. Hackett, J. I. Hall, D. J. Hand, Elizabeth Hardisty, Pauline M. Hark, R. T. Hoohlo, B. C. Hovell, J. K. Howard, N. A. Hutchinson, Jean M. Hynd, Ali Haji Ibrahim, A. S. Jackson, Patricia M. James, I. W. Jamieson, W. P. U. Kennedy, Janet A. King, Sybil F. Kinghorn, Marion J. Lee, Joseph Lewis, Steyn Louw, Phyllis M. Lundie, A. A. A. McCall, Flora E. MacGregor, Catriona MacIntosh, D. S. Mackay, G. H. Mackay, Isobel R. Mackay, Donald MacLean, M. A. MacLeod, D. C. Macmillan, G. P. McMullin, Margaret A. McVicker, C. P. Mayers, Thomas Middlemiss, L. R. Morgan, C. J. Morris, Heather S. Morris, Mary Morrison, Pamela Murray, Elisha Chimbadzwa Mutasa, G. C. Namsoo, Matilda M. Nelson, Rosalind M. Niven, Joanna M. Oliver, Abdool Halleck Mahomed Osman, J. J. B. Petrie, G. E. Philip, J. R. Philip, R. F. Rintoul, M. A. H. Robertson, H. N. Rutherfurd, George Sachs, W. A. Sharman, D. A. Shedden, Anne E. Shepherd, L. F. Slade, C. McG. Small, G. E. Smart, R. W. Smethills, D. Dalrymple-Smith, N. A. Malcolm-Smith, B. H. R. Stack, G. D. Stark, Joh Stuart, M. McD. Tellis, K. W. Thompson, D. J. Turner, G. E. D. Urquhart, D. J. P. N. Van der Minne, J. L. Waddell, A. C. H. Watson, Julie M. Whittle, W. H. Williams, P. Ling Nam Yan.

D.P.H.—N. B. Akim, Frances M. Falconer, Margaret McI. Gilmore, K. E. A. U. Ground, A. D. Macdonald, A. D. McIntyre, Isabella R. Napier, D. M. Pendreigh, E. J. B. Simpson, R. G. Walker.

D.M.R.D.—J. J. Kay-Butler, Q. S. Moore.

Diploma in Medical Services Administration.—J. P. Sexton, J. B. Stolte, H. B. Viefhues.

D.P.M.—W. E. S. Kiernan.

D.T.M. & H.—Sabet Ali, H. M. S. Bristol, Satyanarayana Durvasula, J. T. Millar, Mangalore Kesva Pai, Inder Mohan Rohatgi, Chandeshwa Prasad Sinha, Tin Aung Swe, Win Kyin Taw.

Dr. D. J. McAuliffe has been appointed lecturer in ophthalmology and Dr. W. A. Barr assistant to the pregnancy diagnosis laboratory.

Royal College of Obstetricians and Gynæcologists

At the meeting of council on July 23 with Sir Andrew Claye, the president, in the chair, Mr. Arthur C. H. Bell was elected president and Mr. G. F. Gibberd and Mr. S. W. Maslen-Jones vice-presidents. The following officers were also elected:

Hon. treasurer, Sir John Peel; hon. secretary, Ian M. Jackson; hon. librarian, Arthur J. McNair; hon. curator of the museum, R. Alan Brews; hon. treasurer, Australian regional council, S. Devenish Meares; hon. treasurer, Canadian regional council, G. A. Simpson; hon. treasurer, New Zealand regional council, A. M. Rutherford; hon. treasurer, South African regional council, F. N. Charnock; College representative on the General Medical Council Victor Lack; College representative on the Central Council for District Nursing in London, H. G. E. Arthure.

H. McK. Carey and T. B. Fitzgerald were admitted to the fellowship, and the following were admitted to the membership:

Supriya Chakravorty, F. R. Clark, Bhabesh Chandra Lahiri, K. J. O'Connor, G. R. Sharp.

The following have been elected to the membership:

Mavis F. Anderson, A. A. Armar, J. L. Baker, Christian Bam, Dhirendra Nath Banerjee, Sreemanta Kumar Baneriee, N. A. Beischer, Vishnuprasad Motiram Bhatt, N. M. D. Blyth, Pauline M. Bousquet, A. H. Bradfield, G. F. Bradfield, I. T. Brake, Tancred Busuttil, A. P. Camilleri, I. E. Cary, K. L. Collins, Joan M. Curtis, L. S. Deane, Marie T. D'Netto, R. F. Heys, Ma Hla-Kyi, F. Ponnu Isaiah, W. I. H. Johnston, J. B. Jones, Kurapati Kanakadurgamba, William Kelso, J. F. Kemp, J. F. Leeton, J. L. Marcus, J. M. Mistry, W. M. Moore, E. D. Morris, Barum Kumar Mukherji, Olusola Adewole Ojo, P. R. B. Pedlow, W. S. E. Perera, Walter Pollard, Doreen Rothman, Anjul Kumar Sinha, Sarel Johannes Smal, A. M. Smith, H. J. Solomon, Bruce Sutherland, T. E. Torbet, A. R. Trist, F. W. Van Der Westhuizen, W. L. Whitehouse.

Royal College of Surgeons of Edinburgh

At a meeting of the college on July 22, with Prof. John Bruce, the president, in the chair, the honorary fellowship was conferred upon Prof. J. W. Hinton (New York) and Mr. J. W. T. Dixon and Dr. A. G. Smith were admitted to the fellowship without examination. The following candidates were admitted to the fellowship:

Suresh Vishvanath Bhave, B. J. Carew, Ved Pal Chadha, S. L. Cooke, J. N. Cozens-Hardy, J. R. M. Davidson, Ashit Baran Ramanlal Desai, L. J. De Souza, Arjun Dev, M. S. G. Douglas, Rajat Kumar Dutta, Hari Nandan Prasad Dwivedi, T. A. English, Guan Swee William Fung, Srasht Kumari Ghai, J. R. P. Gibbons, J. I. H. Hadfield, Basil Hessein Helal, Salah El Din Hassan Hosny, Muhammed Akram Hossein, Ivan Jacobson, G. S. Joss, Nickolas Kollitsis, R. A. MacMahon, W. M. McQuillan Kottayam Kadangode Madhavan, Arab Madhavlal Mehta, Guru Prasad Mohanty, M. H. W. Mullerworth, Maung Sein Myint, M. F. Porter, D. J. Reid, G. R. Roberts, R. A. Roxburgh, Mohamed Bayoumi Hassan Sammour, Devindar Paul Sanan, L. P. Seimon, Rohit Jayantilal Shah, Mary P. Shepherd, Ghanshyam Das Singhal, G. G. Smith, D. W. Smith, H. C. Smith, Marthanda Varma Sankaran Valiathan, R. E. Vance, Wilfrid Waldie, D. F. Weirman, C. F. A. Whelan, D. P. C. Williams, Madhav Yeshwant Wipat.

International Society of Tropical Dermatology

This society was inaugurated at a meeting held in the Rockefeller Institute, New York City, on May 10, when Prof. Aldo Castellani gave the presidential address. Dr. Frederick Reiss, the secretary-general, said that fifty countries are represented in the society, which has almost 1300 charter members. The first international congress is likely to be in 1962 or 1963.

"Spiritual Healers" in Hospitals

On July 20 the East Anglian Regional Hospital Board by 11 votes to 3 decided to support the British Medical Association's resolution that members of the National Federation of Spiritual Healers should not be allowed to practise in National Health Service hospitals (*East Anglian Daily Times*, July 21, 1960). Hospital management committees in the region are to be informed.

New Social Security Arrangement with Switzerland

A social security agreement which the United Kingdom concluded last November with Switzerland has been ratified and came into force on July 1.

It supplements the provisions of the existing agreement and will enable United Kingdom nationals to draw Swiss non-contributory pensions if they have lived in Switzerland for 15 years. It also provides that people who are insured for sickness benefit in either country may qualify for sickness benefit as soon as they become insured in the other country. Visitors to Switzerland will not receive free medical treatment there by virtue of the agreement.

International Symposium on Fleming's Lysozyme

This symposium will be held from April 7 to 9, 1961, in Milan. Further particulars may be had from the organising committee, Via Modica 6, Milan, Italy.

Rockefeller Foundation Grants

During the second quarter of 1960 the Foundation distributed $8,263,908. Grants for medical and natural sciences amounted to $3,949,058. The grants include a five-year grant of $288,000 to the University College of the West Indies, Jamaica, for research and training especially designed to meet the medical problems of the Caribbean; and a three-year grant of £50,000 (about $142,500) to the Ministry of Health, Nairobi, to improve the training of health workers for village medical centres in Kenya.

New Telephone for the Hard of Hearing

The Post Office announce that a new hearing-aid telephone is now available.

The hearing-aid is a small transistorised amplifier which is fitted in the handset portion of the telephone. It replaces the battery-type equipment, which was in a separate box. Volume is controlled by a finger wheel fitted in the earpiece. Additional rental for the aid is 15*s*. a quarter (the same as for the old battery equipment). Application should be made to the local telephone manager.

Dental Ancillaries

By ensuring that a sufficient number of pupils in need of dental treatment are sent from schools in the area, the London County Council is cooperating with the General Dental Council in its experimental scheme to train dental ancillaries at a centre to be established in the grounds of New Cross General Hospital.

The new training school will take 60 women students annually and the course will last two years. The students will begin to treat children during their second year and they will work under the supervision of qualified dental surgeons. Dentists working for the L.C.C. will be attached to the clinic to complete treatment where students cannot do all that is necessary. Parents will be free to decide whether they wish their children to attend the clinic, and some of the L.C.C.'s ordinary clinics in the area will be kept open if staff is available. The whole cost will be borne by the General Dental Council, except that the L.C.C. will pay dentists appointed for work at the new clinic.

The teachers' associations which were consulted about the scheme objected that it it would cause excessive interruption and loss of school time. The education and health committees of the L.C.C., however, think that the scheme will demonstrate the value of ancillaries to the community, that the teeth of London schoolchildren will benefit, and that in time other parts of the country will benefit too.

Lord Boyd Orr and Dr. D. P. Cuthbertson have been elected honorary members of the American Institute of Nutrition.

Sir Solly Zuckerman has been appointed a member of the academic planning board which is to advise the Norwich University Promotion Committee.

Colonel G. M. Warrack is to succeed Brigadier W. R. Ward as adviser to the director-general, Army Medical Services, on Territorial Army matters.

The West Riding Edinburgh Graduates Association would welcome new members. The secretary is Mr. James S. Davidson, 1, Ashburnham Grove, Bradford, 9.

The Chartered Society of "Queen Square" will shortly fill vacant pensions (£20 per annum). Patients with incurable nervous disease are eligible. Further particulars may be had from the society, 11, Queen Court, Queen Square, London, W.C.1.

The Dan Mason Research Committee, which in 1956 published a survey of the *Work of Recently Qualified Nurses* has now inquired into the work, responsibilities, and status of the staff nurse. This report (5*s*.) may be had from the National Florence Nightingale Memorial Committee of Great Britain and Northern Ireland, 7, Grosvenor Crescent, London, S.W.1.

A draft British Standard for Spencer Wells artery forceps (straight and curved) with box joints has been drawn up. Comments on this specification (AA [SGC]291) should be sent before Aug. 25 to Mr. W. S. Hodges, secretary of technical committee SGC/3, British Standards Institution, 2, Park Street, London, W.1.